EUROPEAN PATENT OFFICE

Patent Abstracts of Japan

PUBLICATION NUMBER : 2004203871
PUBLICATION DATE : 22-07-04

APPLICATION DATE : 12-12-03
APPLICATION NUMBER : 2003414006

APPLICANT : YAMANOUCHI PHARMACEUT CO LTD;

INVENTOR : NAKAMURA HARUKA;

INT.CL. : C07D213/81 A61K 31/4375 A61K 31/4418 A61K 31/4439 A61K 31/444 A61K 31/4523 A61K 31/4545 A61K 31/4725 A61K 31/496 A61K 31/497

TITLE : MEDICINAL COMPOSITION

ABSTRACT : PROBLEM TO BE SOLVED: To provide a medicinal composition useful for preventing and treating respiratory diseases associated with 4-type phosphodiesterase, especially, bronchial asthma, chronic obstructive pulmonary disease and the like.

SOLUTION: A pyridine derivative or its salt having each of a phenyl which may be substituted with an alkoxy or the like at 6 position, and an N-containing heterocycle-carbonyl group bonded at 2-position with an N-substituted carbamoyl group or N-atom, is investigated to have strong and selective inhibition action to the 4-type phosphodiesterase and found to be useful as a medicinal agent.

COPYRIGHT: (C)2004,JPO&NCIPI

(19)日本国特許庁(JP)　(12)公開特許公報(A)　(11)特許出願公開番号
特開2004-203871
(P2004-203871A)
(43)公開日　平成16年7月22日(2004.7.22)

(51)Int.Cl.[7]	F I		テーマコード（参考）
C07D 213/81	C07D	213/81	4C055
A61K 31/4375	A61K	31/4375	4C063
A61K 31/4418	A61K	31/4418	4C065
A61K 31/4439	A61K	31/4439	4C086
A61K 31/444	A61K	31/444	

審査請求 未請求　請求項の数 12　ＯＬ　（全 58 頁）　最終頁に続く

(21)出願番号　特願2003-414006(P2003-414006)
(22)出願日　平成15年12月12日(2003.12.12)
(31)優先権主張番号　特願2002-361550(P2002-361550)
(32)優先日　平成14年12月13日(2002.12.13)
(33)優先権主張国　日本国(JP)

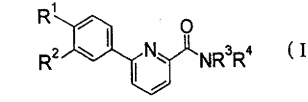
(71)出願人　000006677
山之内製薬株式会社
東京都中央区日本橋本町２丁目３番１１号
(74)代理人　100089200
弁理士　長井　省三
(74)代理人　100098501
弁理士　森田　拓
(74)代理人　100109357
弁理士　矢野　恵美子
(72)発明者　岩田　正洋
茨城県つくば市御幸が丘　２１　山之内製薬株式会社内
(72)発明者　河野　剛征
茨城県つくば市御幸が丘　２１　山之内製薬株式会社内

最終頁に続く

(54)【発明の名称】医薬組成物

(57)【要約】
【課題】　４型ホスホジエステラーゼが関与する呼吸器疾患、殊に気管支　息や慢性閉塞性肺疾患等の予防・治療に有用な医薬組成物を提供すること。
【解決手段】　６位にアルコキシ基等で置換されていてもよいフェニル基を、２位にＮ－置換カルバモイル基又は窒素原子で結合する含窒素ヘテロ環－カルボニル基をそれぞれ有するピリジン誘導体又はその塩が、強力且つ選択的な４型ホスホジエステラーゼ阻害活性を有することを知見し、医薬上有用であることを見出した。
【選択図】　なし

【特許請求の範囲】
【請求項１】
一般式（Ｉ）で示されるピリジン誘導体又はその製薬学的に許容される塩と、製薬学的に許容される担体とからなる医薬組成物。
【化１】



（Ｉ）

（式中の記号は以下の意味を示す。
R^1及びR^2：同一又は互いに異なって、Ｈ、ハロゲン、低級アルキル、Ｏ低級アルキル、Ｏ（ハロゲンで置換された低級アルキル）、NH_2、ＮＨ低級アルキル、Ｎ（低級アルキル）$_2$、ＮＨＣＯ低級アルキル、Ｏ低級アルキレンＮＨ低級アルキル、Ｏ低級アルキレンＮ（低級アルキル）$_2$、Ｏ低級アルキレンCO_2R^0、Ｏ低級アルキレン炭化水素環又はＯ低級アルキレンヘテロ環、或いはR^1及びR^2が一体となってＯ低級アルキレンＯ、
R^0：Ｈ、低級アルキル又はCH_2（置換されていてもよい）フェニル、
R^3：低級アルケニル、低級アルキニル、置換されていてもよい炭化水素環、置換されていてもよいヘテロ環、低級アルキレン置換されていてもよい炭化水素環、低級アルキレン置換されていてもよいヘテロ環、低級アルキレンR^{51}、低級アルキレンCO_2R^0、低級アルキレン$N(R^0)$低級アルキル、$C(R^{53})(R^{54})R^{55}$、低級アルキレン$C(R^{53})(R^{54})R^{55}$又はＯR^0、
R^4：Ｈ、低級アルキル、低級アルケニル、低級アルキニル、置換されていてもよい炭化水素環、置換されていてもよいヘテロ環、低級アルキレン置換されていてもよい炭化水素環、低級アルキレン置換されていてもよいヘテロ環、低級アルキレンR^{51}、低級アルキレンCO_2R^0、低級アルキレン$N(R^0)$低級アルキル、$C(R^{53})(R^{54})R^{55}$又は低級アルキレン$C(R^{53})(R^{54})R^{55}$、
R^{51}：ＣＯ低級アルキル、ＣＯ（置換されていてもよい炭化水素環）、ＣＯ（置換されていてもよいヘテロ環）、ＣＯ低級アルキレン（置換されていてもよい炭化水素環）、ＣＯ低級アルキレン（置換されていてもよいヘテロ環）、ＣＮ、ＯＨ、Ｏ低級アルキル、Ｏ（置換されていてもよい炭化水素環）、Ｏ（置換されていてもよいヘテロ環）、Ｏ低級アルキレン（置換されていてもよい炭化水素環）、Ｏ低級アルキレン（置換されていてもよいヘテロ環）、Ｓ低級アルキル、Ｓ（置換されていてもよい炭化水素環）、Ｓ（置換されていてもよいヘテロ環）、Ｓ低級アルキレン（置換されていてもよい炭化水素環）、Ｓ低級アルキレン（置換されていてもよいヘテロ環）、$NH(R^0)$、$N(CH_3)_2$、$N(C_2H_5)_2$、$N(R^0)$（置換されていてもよい炭化水素環）、$N(R^0)$（置換されていてもよいヘテロ環）、$N(R^0)$低級アルキレン（置換されていてもよい炭化水素環）、$N(R^0)$低級アルキレン（置換されていてもよいヘテロ環）、$N(R^0)$ＣＯ低級アルキル、$N(R^0)$ＣＯ（置換されていてもよい炭化水素環）、$N(R^0)$ＣＯ（置換されていてもよいヘテロ環）、$N(R^0)$ＣＯ低級アルキレン（置換されていてもよい炭化水素環）、$N(R^0)$ＣＯ低級アルキレン（置換されていてもよいヘテロ環）、$N(R^0)$ＣＯＯ低級アルキル、$N(R^0)$ＣＯＯ低級アルキレン（置換されていてもよい炭化水素環）又は$N(R^0)$ＣＯＯ低級アルキレン（置換されていてもよいヘテロ環）、
R^{53}、R^{54}及びR^{55}：同一又は互いに異なって、Ｈ、低級アルキル、CO_2R^0、$CON(R^0)(R^{56})$、R^{51}、又はR^{58}、
R^{56}：置換されていてもよい炭化水素環、置換されていてもよいヘテロ環、低級アルキレン置換されていてもよい炭化水素環、低級アルキレン置換されていてもよいヘテロ環、低級アルキレンR^{51}又は低級アルキレンCO_2R^0、
或いは、NR^3R^4において、R^3とR^4が結合する Ｎと一体となって、置換されていてもよい含

窒素ヘテロ環。

但し、以下の化合物を除く：

(1) R^4が$C_{1\ 6}$アルキル、$C_{3\ 7}$シクロアルキル、$C_{1\ 4}$アルキレン フェニル、フェニル、ピリジル、ピリミジル、チアゾリル、又はオキサゾリルのとき、R^3が$C_{1\ 6}$アルキル、($C_{1\ 4}$アルキル又はハロゲンで置換されていてもよい)フェニル)、$CH(R^{00})CO_2R^{00}$、$C_{3\ 7}$シクロアルキル、$C_{1\ 4}$アルキレン フェニル、$C_{2\ 5}$アルキレン $N(CH_3)(C_4H_9)$、$C_{2\ 5}$アルキレン $N(C_2H_5)(C_3H_7)$、ピリジル、ピリミジル、チアゾリル、オキサゾリル或いはテトラゾリルである化合物、及び、

(2) R^4がHのとき、R^3がOH、$C_{1\ 6}$アルキル、($C_{1\ 4}$アルキル又はハロゲンで置換されていてもよいフェニル)、$CH(R^{00})CO_2R^{00}$、$C_{3\ 7}$シクロアルキル、$C_{1\ 4}$アルキレン フェニル、$C_{2\ 5}$アルキレン $N(CH_3)(C_4H_9)$、$C_{2\ 5}$アルキレン $N(C_2H_5)(C_3H_7)$、ピリジル、ピリミジル、チアゾリル、オキサゾリル或いはテトラゾリルである化合物、及び、

(3) NR^3R^4において、R^3とR^4が結合するNと一体となって形成する含窒素ヘテロ環が、(i) 1乃至2個の$C_{1\ 4}$アルキル、CO_2R^{00}、$CONH_2$、$CON(CH_3)_2$、オキソ、OH、NH_2又は$N(CH_3)_2$で置換されていてもよく、不飽和化されていてもよい、1ピロリジル又は1ピペリジル：(ii) 不飽和化されていてもよい、4モルホリニル又はチオモルホリン 4イル：(iii) 4位がメチル、アセチル又はベンジルで置換されていてもよく、不飽和化されていてもよい、1ピペラジル：又は、(iv) Fで置換されていてもよいキノリン環、である化合物。)

【請求項２】

4型ホスホジエステラーゼ阻害剤である請求項１記載の医薬組成物。

【請求項３】

呼吸器疾患の予防又は治療剤である請求項２記載の医薬組成物。

【請求項４】

気管支喘息の予防又は治療剤である請求項３記載の医薬組成物。

【請求項５】

慢性閉塞性肺疾患(COPD)の予防又は治療剤である請求項３記載の医薬組成物。

【請求項６】

ピリジン誘導体が、4(4{4[6(3,4ジメトキシフェニル)ピリジン2カルボニル]ピペラジン1イル}フェニル)モルホリンである請求項１記載の医薬組成物。

【請求項７】

固形製剤である請求項６記載の医薬組成物。

【請求項８】

4(4{4[6(3,4ジメトキシフェニル)ピリジン2カルボニル]ピペラジン1イル}フェニル)モルホリンの結晶。

【請求項９】

粉末X線回折で2θ(°)10.82、12.86、16.96、19.90、21.76及び22.88のピークを有する請求項８記載の結晶。

【請求項１０】

粉末X線回折で2θ(°)11.66、14.92、16.92、19.44、20.10、21.06及び21.90のピークを有する請求項８記載の結晶。

【請求項１１】

DSC分析で140～143℃に熱吸収ピーク(補外開始温度(オンセット))を有する請求項８記載の結晶。

【請求項１２】

DSC分析で128～131℃に熱吸収ピーク(補外開始温度(オンセット))を有する請求項８記載の結晶。

【発明の詳細な説明】

【技術分野】

【０００１】

本発明は、フェニルピリジン誘導体を有効成分とする医薬、特に4型ホスホジエステラ

ーゼ（PDE4）阻害剤に関する。

【背景技術】

【０００２】

これまで気道の可逆的閉塞とされてきた　息は、現在では、多くの炎症細胞が関与する慢性気道炎症に基づく気道過敏・気道閉塞を特徴とする疾患としてとらえられるようなった。その患者数はこれまで増加の一途をたどっており、今後もさらに増えることが予想される。

息の治療には現在、抗炎症薬として吸入ステロイド薬が、また気管支拡張薬としてアドレナリン等のβ刺激薬及びアミノフィリンやテオフィリン等のキサンチン誘導体が主に使用されている。

吸入ステロイド薬は、広範な抗炎症作用を有し、　息治療薬としての有用性は高いが、適切な吸入方法の指導が必要であることやステロイド抵抗性の　息患者の存在などが指摘されている（ASTHMA 13 1. 69 73 (2000). 内科　81. 485 490 (1998)）。

気管支拡張薬は、気道平滑筋において細胞内アデノシン3'.5' サイクリックーリン酸（cAMP）の産生酵素であるアデニル酸シクラーゼを活性化し、あるいはcAMPの分解酵素であるホスホジエステラーゼ（PDE）を阻害することにより細胞内のcAMP濃度を上昇させ、気道平滑筋の収縮を緩解するものである（内科　69. 207 214 (1992)）。細胞内cAMP濃度の上昇は、気道平滑筋では収縮の抑制を引き起こすことが知られており（Clin. Exp. Aller 9y. 22. 337 344 (1992)、Drugs of the Future. 17. 799 807 (1992)）、　息症状の改善に有効である。

しかしながら、キサンチン誘導体は血圧降下や強心作用等の全身性副作用を発現すること（J. Cyclic Nucleotide and Protein Phosphorylation Res.. 10. 551 564 (1985)、J. Pharmacol. Exp. Ther.. 257. 741 747 (1991)）、また、β刺激薬は脱感作を生じやすく、使用量が増加すると手指振戦、動　等の副作用を生ずることが知られている。

【０００３】

一方、慢性閉塞性肺疾患（COPD）は、異常な炎症性反応と関連する可逆的ではない気流制限を特徴とする呼吸器疾患であり、現在、世界の死亡原因の第4位であるとされている（Executive summary. Global Initiative for Chronic Obstructive Lung Disease (GOLD). (2000)）。COPDに対する薬物療法としては、現在、　息と同様、β刺激薬や抗コリン薬、アミノフィリンやテオフィリン等のキサンチン誘導体といった気管支拡張薬が一般的に使用されている。また、COPDにおいても気道における慢性炎症の存在が閉塞性障害に大きく関与していることが注目されていることから吸入ステロイド薬も使用されるが、吸入ステロイドによる継続的治療はCOPD患者のFEV1（forced expiratory volume in one second）の長期低下を改善しないことが報告されており（N. Engl. J. Med. 340. 1948 53 (1999)、Lancet 353. 1819 23 (1999)、BMJ 320. 1297 303 (2000)、N. Engl. J. Med. 343. 1902 9 (2000)）、COPDの病態を改善しうる抗炎症薬が切望されている。

【０００４】

PDEは少なくともPDE1～9のファミリーに分類され、それぞれ分布又は機能に違いがあることが解明されてきた（Proc. Nucleic Acid Res. Mol. Biol. 63. 1 38 (1999)）。特にPDE4は、スクレオチドの中でもアデノシン3'.5' サイクリックーリン酸（cGMP）に作用することなく、cAMPを特異的に分解するものであり、気道平滑筋及び浸潤細胞の両者でその存在が認められている。

PDE4阻害剤は、モルモットにおける抗原及び血小板活性化因子による好酸球浸潤に対し、抑制作用を示し（Eur. J. Pharmacol.. 255. 253 256 (1994)）、好酸球からの障害性蛋白（MBP、ECP）の遊離を抑制する（Br. J. Pharmacol.. 115. 39 47(1995)）ことが報告されている。さらに収縮物質（ヒスタミン、メサコリン、LTD_4）による気道平滑筋の収縮に対し抑制作用を示すこと（Br. J. Pharmacol.. 113. 1423 1431 (1994)）、　息に深く関与すると言われているサイトカインであるIL 4の産生を阻害すること（J. Invest. Dermatol.. 100. 681 684 (1993)）、気道における血管透過性の　進に対して抑制作用を発現すること（Fundam. Clin. Pharmacol.. 6. 247 249 (1992)）、気道過敏症に対して

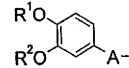
抑制作用を示すこと（Eur. J. Pharmacol.. 275. 75 82 (1995)）が報告されている。よって、PDE4阻害剤は　息治療剤として期待されている。

さらにPDE4阻害薬は、COPDにおける気道炎症に関与しているとされる好中球に対し浸潤抑制作用を有すること(Pulm. Pharmacol. Ther. 2001 Mar; 14(2): 157 164)が報告され、また、臨床試験においてもPDE4阻害薬は、COPD患者の呼吸機能を改善しうることが示され(Clin. Exp. Allergy. 1999 Jun; 29 Suppl 2: 99 109)、COPD治療薬としても期待されている。

【０００５】

特許文献１には、PDE4阻害活性を有する化合物として下記化合物が開示されている。

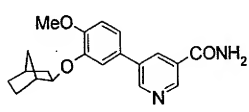
【化２】



〔式中、A、Y及びBは結合等を、ZはR³で置換されていてもよいピリジン環等を、R³はCONR⁴R⁵等を意味し、R⁴はH、$C_{1\ 6}$アルキル、$C_{1\ 4}$アルキルもしくはハロゲンで置換されていてもよいフェニル、CH(R⁷)CO_2R^6、$C_{3\ 7}$シクロアルキル、$C_{1\ 4}$アルキレン フェニル又は$C_{2\ 5}$アルキレン ジアルキルアミノ(当該ジアルキルアミノ部は炭素数が全部で５個以下)、R⁵はH、$C_{1\ 6}$アルキル、$C_{3\ 7}$シクロアルキル、$C_{1\ 4}$アルキレン フェニル、フェニル、ピリジル、ピリミジル、チアゾリル又はオキサゾリル、或いはR⁴及びR⁵は結合する窒素原子とともに(1)１乃至２個の$C_{1\ 4}$アルキル、CO_2R^7、$CONH_2$、$CON(CH_3)_2$、オキソ、OH、NH_2及びN(CH_3)₂から選択される基で置換されていてもよい、飽和又は不飽和５～６員ヘテロ環、(2)環原子として更に、O、S、N(H)、N(CH_3)、N($COCH_3$)又はN(CH_2Ph)から選択される１個のヘテロ原子を有する飽和又は不飽和６員ヘテロ環、あるいは(3)フッ素で置換されていてもよいキノリン環を示す。〕

しかしながら、当該公報の広範なクレームにはフェニルピリジンカルボキサミド誘導体を含むものの、具体的に記載のある化合物は、下記の5 フェニルピリジン 3 カルボキサミドのみである。

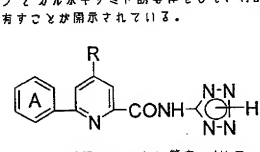
【化３】



【０００６】

６フェニルピリジン２カルボキサミド誘導体として、特許文献２には、下記化合物が抗アレルギー作用を有すことが開示されている。

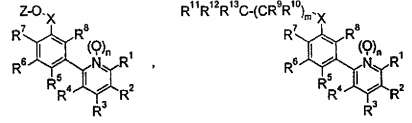
【化４】



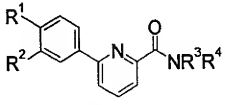
（式中、Rは水素、ハロゲン、低級アルコキシ等を、Aはフェニル、ハロゲン、低級アルキル、低級アルコキシ、ニトロ及びOHから選択される置換基を１～３有するフェニル基を示す。）

しかしながら、当該化合物のPDE4阻害活性に関する記載は無い。

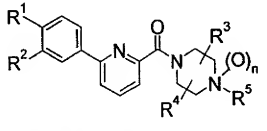
【０００７】
また、特許文献３及び特許文献４に、除草作用及び植物の乾燥作用を有する下記フェニルピリジンカルボキサミド誘導体が開示されているが、PDE4阻害作用に関しては開示も示唆もない。
【化５】



（式中、R^1はCONH$_2$、CONH(C_{1-4}アルキル)、CON(C_{1-4}アルキル)$_2$等を示す。他は当該公報参照。）
【０００８】
PDE4阻害活性を有するフェニルピリジンカルボキサミド誘導体として、特許文献５に下記化合物
【化６】



（式中、R^1及びR^2はH、ハロゲン、低級アルキル、O低級アルキル等、R^3は低級アルケニル等、R^4はH、低級アルキル等、或いはNR^3R^4において、R^3とR^4が結合するNと一体となって、置換されていてもよい含窒素ヘテロ環を示す。詳細は当該公報参照。）が、特許文献６に下記化合物
【化７】



（式中、R^1及びR^2はH、ハロゲン、低級アルキル、O低級アルキル等、R^5はH、低級アルキル等を示す。詳細は当該公報参照。）が、それぞれ開示されているものの、特許文献５及び６はいずれも本願優先日後に公開された文献である。
【０００９】
【特許文献１】国際公開第９４／１２４６１号パンフレット
【特許文献２】特開昭５６－７７８２号公報
【特許文献３】国際公開第９６／２１６４５号パンフレット
【特許文献４】国際公開第９６／２１６４６号パンフレット
【特許文献５】特開２００３－６４０５７号公報
【特許文献６】国際公開第０２／１０２７７８号パンフレット
【発明の開示】

【発明が解決しようとする課題】

【００１０】

本発明者等は、経口投与可能で、PDE4を良好かつ選択的に阻害し、副作用の少ない気管支　息、COPD等の呼吸器疾患の予防・治療に有用な医薬組成物を提供すること、さらにはこれらを含有する医薬を提供することを目的として研究を行った。

【課題を解決するための手段】

【００１１】

本発明者等は、PDE4に対して阻害活性を有する化合物につき鋭意検討した。その結果、6位にフェニル基を有する新規なピリジン２カルボキサミド誘導体が強力かつ選択的なPDE4阻害作用を有することを知見し、本発明を完成した。

【発明の効果】

【００１２】

後記式（Ｉ）で示される6位にフェニル基を有する新規なピリジン２カルボキサミド誘導体はPDE4の阻害活性に優れていることから、当該化合物を含有する医薬組成物は、PDE4が関与する呼吸器疾患（例えば気管支　息（アトピー性　息を含む）、COPD、慢性気管支炎、肺炎性疾患、成人呼吸窮迫症候群（ARDS）等）の予防・治療剤として有用である。特に気管支　息及びCOPDの予防・治療薬として期待できる。また、当該医薬組成物は、PDE4の関与が知られているその他の疾患、例えばはサイトカイン（IL１、IL４、IL８及びTNF（腫　壊死因子））等の関与する疾患（例えば、関節リウマチ、潰　性大腸炎、クローン病、敗血症、敗血症性ショック、内毒素性ショック、グラム陰性菌性敗血症、トキシックショック症候群、腎炎、肝炎、感染（細菌及びウイルス）、循環不全（心不全、動脈硬化、心筋梗塞、脳卒中）等）等の予防・治療薬としても有用である。

更に、本発明の4（4［6（3.4ジメトキシフェニル)ピリジン２カルボニル]ピペラジン１イル)フェニル)モルホリンの結晶、特にα型及びβ型結晶は安定性に優れ、本発明の医薬組成物の製造原体として有用である。中でもβ型結晶は工業的生産における大量合成に適している。

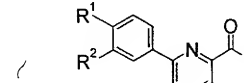
【発明を実施するための最良の形態】

【００１３】

即ち、本発明は、下記一般式（Ｉ）で示される新規なピリジン誘導体又はその製薬学的に許容される塩と製薬学的に許容される担体とからなる医薬組成物、殊に気管支　息やCOPD等の予防・治療薬として有効な医薬組成物に関する。

【００１４】

【化８】



（Ｉ）

（式中の記号は以下の意味を示す。

R^1及びR^2：同一又は互いに異なって、H、ハロゲン、低級アルキル、O低級アルキル、O（ハロゲンで置換された低級アルキル）、NH_2、NH低級アルキル、N(低級アルキル)$_2$、NHCO低級アルキル、O低級アルキレンNH低級アルキル、O低級アルキレンN(低級アルキル)$_2$、O低級アルキレンCO_2R^0、O低級アルキレン炭化水素環又はO低級アルキレンヘテロ環、或いはR^1及びR^2が一体となって O低級アルキレンO、

R^0：H、低級アルキル又はCH_2（置換されていてもよいフェニル）、

R^3：低級アルケニル、低級アルキニル、置換されていてもよい炭化水素環、置換されていてもよいヘテロ環、低級アルキレン置換されていてもよい炭化水素環、低級アルキレン．置換されていてもよいヘテロ環、低級アルキレンR^{51}、低級アルキレンCO_2R^0、低級

アルキレン $N(R^0)$ 低級アルキル、$C(R^{53})(R^{54})R^{55}$、低級アルキレン $C(R^{53})(R^{54})R^{55}$又はOR^0、

R^4：H、低級アルキル、低級アルケニル、低級アルキニル、置換されていてもよい炭化水素環、置換されていてもよいヘテロ環、低級アルキレン 置換されていてもよい炭化水素環、低級アルキレン 置換されていてもよいヘテロ環、低級アルキレン R^{51}、低級アルキレン CO_2R^0、低級アルキレン $N(R^0)$ 低級アルキル、$C(R^{53})(R^{54})R^{55}$又は低級アルキレン $C(R^{53})(R^{54})R^{55}$、

R^{51}：CO 低級アルキル、CO（置換されていてもよい炭化水素環）、CO（置換されていてもよいヘテロ環）、CO 低級アルキレン（置換されていてもよい炭化水素環）、CO 低級アルキレン（置換されていてもよいヘテロ環）、CN、OH、O 低級アルキル、O（置換されていてもよい炭化水素環）、O（置換されていてもよいヘテロ環）、O 低級アルキレン（置換されていてもよい炭化水素環）、O 低級アルキレン（置換されていてもよいヘテロ環）、S 低級アルキル、S（置換されていてもよい炭化水素環）、S（置換されていてもよいヘテロ環）、S 低級アルキレン（置換されていてもよい炭化水素環）、S 低級アルキレン（置換されていてもよいヘテロ環）、$NH(R^0)$、$N(CH_2)_2$、$N(C_2H_5)_2$、$N(R^0)$（置換されていてもよい炭化水素環）、$N(R^0)$（置換されていてもよいヘテロ環）、$N(R^0)$ 低級アルキレン（置換されていてもよい炭化水素環）、$N(R^0)$（置換されていてもよいヘテロ環）、$N(R^0)$ 低級アルキレン（置換されていてもよいヘテロ環）、$N(R^0)CO$ 低級アルキル、$N(R^0)CO$（置換されていてもよい炭化水素環）、$N(R^0)CO$（置換されていてもよいヘテロ環）、$N(R^0)CO$ 低級アルキレン（置換されていてもよい炭化水素環）、$N(R^0)CO$ 低級アルキレン（置換されていてもよいヘテロ環）、$N(R^0)CO$ O 低級アルキル、$N(R^0)CO$ O 低級アルキレン（置換されていてもよい炭化水素環）又は$N(R^0)CO$ O 低級アルキレン（置換されていてもよいヘテロ環）、

R^{53}、R^{54}及びR^{55}：同一又は互いに異なって、H、低級アルキル、CO_2R^0、$CON(R^0)(R^{56})$、R^{51}、又はR^{58}、

R^{56}：置換されていてもよい炭化水素環、置換されていてもよいヘテロ環、低級アルキレン 置換されていてもよい炭化水素環、低級アルキレン 置換されていてもよいヘテロ環、低級アルキレン R^{51}又は低級アルキレン CO_2R^0、

或いは、NR^3R^4において、R^3とR^4が結合するN と一体となって、置換されていてもよい含窒素ヘテロ環。

但し、以下の化合物を除く：

(1) R^4が$C_{1\text{-}6}$アルキル、$C_{3\text{-}7}$シクロアルキル、$C_{1\text{-}4}$アルキレン フェニル、フェニル、ピリジル、ピリミジル、チアゾリル、又はオキサゾリルのとき、R^3が$C_{1\text{-}6}$アルキル、($C_{1\text{-}4}$アルキル又はハロゲンで置換されていてもよいフェニル)、$CH(R^{00})CO_2R^{00}$、$C_{3\text{-}7}$シクロアルキル、$C_{1\text{-}4}$アルキレン フェニル、$C_{2\text{-}5}$アルキレン $N(CH_3)(C_6H_5)$、或いは$C_{2\text{-}5}$アルキレン $N(C_2H_5)(C_6H_5)$である化合物（R^{00}は、同一又は互いに異なってH又は$C_{1\text{-}4}$アルキル。）、

(2) R^4がHのとき、R^3がOH、$C_{1\text{-}6}$アルキル、($C_{1\text{-}4}$アルキル又はハロゲンで置換されていてもよい)フェニル、$CH(R^{00})CO_2R^{00}$、$C_{3\text{-}7}$シクロアルキル、$C_{1\text{-}4}$アルキレン フェニル、$C_{2\text{-}5}$アルキレン $N(CH_3)(C_6H_5)$、$C_{2\text{-}5}$アルキレン $N(C_2H_5)(C_6H_5)$、ピリジル、ピリミジル、チアゾリル、オキサゾリル或いはテトラゾリルである化合物、及び、

(3) NR^3R^4において、R^3とR^4が結合するN と一体となって形成する含窒素ヘテロ環が、(i) 1乃至2個の$C_{1\text{-}4}$アルキル、CO_2R^{00}、$CONH_2$、$CON(CH_3)_2$、オキソ、OH、NH_2又は$N(CH_2)_2$で置換されていてもよく、不飽和化されていてもよい、1 ピロリジル又は1 ピペリジル：(ii) 不飽和化されていてもよい、4 モルホリニル又はチオモルホリン 4 イル：(iii) 4位がメチル、アセチル又はベンジルで置換されていても良く、不飽和化されていてもよい、1 ピペラジル：又は、(iv) Fで置換されていてもよいキノリン環、である化合物。以下同様。）

上記一般式（I）で示される化合物において、特に4 (4 {4 [8 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェニル)モルホリン（以下、「化合物A」と表記する場合がある）が好ましく、更に、化合物Aには2種の結晶多形が存在し、意

外にもいずれの結晶も本発明医薬組成物の製造原体として好適であることを見出した。本発明はこれらの結晶をも包含する。

【００１５】

以下、本発明を詳細に説明する。

本明細書中、「アルキル」、「アルケニル」、「アルケニレン」、「アルキニル」及び「アルキニレン」とは、直鎖状又は分枝状の炭化水素鎖を意味する。「低級アルキル」は、好ましくは炭素数１～６個のアルキル基であり、より好ましくは炭素数１～４個のアルキル基、更に好ましくはメチル及びエチルである。「低級アルキレン」は、上記「低級アルキル」の任意の水素原子１個を除去してなる二価基を意味し、好ましくは炭素数１～４個のアルキレンであり、より好ましくはメチレン、エチレン及びプロピレンである。「低級アルケニル」は、炭素数２以上の「低級アルキル」の任意の位置に、１個以上の二重結合を有する基を意味し、好ましくは炭素数２～４個のアルケニルである。「低級アルケニレン」は、炭素数２以上の「低級アルキレン」の任意の位置に、１個以上の二重結合を有する基を意味し、好ましくは炭素数２～４個のアルケニレンである。「低級アルキニル」は、炭素数２以上の「低級アルキル」の任意の位置に、１個以上の三重結合を有する基を意味し、好ましくは炭素数２～４個のアルキニルである。「低級アルキニレン」は、炭素数２以上の「低級アルキレン」の任意の位置に、１個以上の三重結合を有する基を意味し、好ましくは炭素数２～４個のアルキニレンである。

「ハロゲン」は、F、Cl、Br及びIを示す。「ハロゲンで置換された低級アルキル」とは、好ましくは、１個以上のハロゲンで置換された炭素数１～６個のアルキルを意味し、より好ましくは１個以上のFで置換されたC$_{1-6}$アルキルであり、更に好ましくは、フルオロメチル、ジフルオロメチル、トリフルオロメチル及びトリフルオロエチルである。

【００１６】

「炭化水素環」は、炭素数3から14個の単環～三環式の炭化水素環基を意味し、シクロアルキル、シクロアルケニル及び芳香族炭化水素、並びに、架橋されたシクロアルキル及びスピロ環を含む。またそれらが互いに縮合し、インダニルやテトラヒドロナフチル等を形成していてもよい。

「シクロアルキル」は、好ましくは炭素数３～８個のシクロアルキルであり、より好ましくはシクロプロピル、シクロペンチル及びシクロヘキシルである。「シクロアルケニル」は、好ましくは炭素数５～８個のシクロアルケニルであり、より好ましくはシクロヘキセニルである。「芳香族炭化水素」は、炭素数６～14個の芳香族炭化水素基を意味し、好ましくはフェニル及びナフチルであり、より好ましくはフェニルである。「架橋されたシクロアルキル」としては、好ましくはノルボルニル及びアダマンチルである。

【００１７】

「ヘテロ環」は、環原子として0、S及びNから選択されるヘテロ原子を１乃至４個含有する飽和又は不飽和の単環３～８員、好ましくは５～７員ヘテロ環であり、当該ヘテロ環同士、又はシクロアルキル環やベンゼン環と縮環し二から三環式ヘテロ環を形成してもよい。環原子であるSは1又はN が酸化されオキシドやジオキシドを形成してもよい。当該ヘテロ環は飽和ヘテロ環、芳香族ヘテロ環及びその部分的に飽和されたヘテロ環を含み、飽和ヘテロ環及び部分的に飽和されたヘテロ環においては任意の炭素原子がオキソ基で置換されていてもよい。また、当該ヘテロ環は、架橋されていてもよく、スピロ環を形成してもよい（オキソ基より誘導される1.3 ジオキソラン環等のアセタール体を含む）。該ヘテロ環は好ましくは５乃至７員飽和又は不飽和単環ヘテロ環基であり、より好ましくは、ピロリジン、ピリジン、ピペリジン、モルホリン、チオフェン、チアゾール、イミダゾール、テトラゾール、ピラゾール及びピペラジンである。「含窒素ヘテロ環」とは、上記「ヘテロ環」において、環原子として１個以上のN原子を有するヘテロ環基を示し、好ましくは５乃至７員飽和単環ヘテロ環基であり、より好ましくはピロリジン、ピペリジン、モルホリン及びピペラジン、更に好ましくはピペラジンである。

【００１８】

「置換されていてもよい」とは、「無置換」あるいは「同一又は異なる置換基を１～５

個有していること」を示す。

「置換されていてもよい含窒素ヘテロ環」における置換基は、好ましくは、低級アルキル、ハロゲン、OH、NH_2、$N(R^0)$低級アルキル、CO_2R^0、$CONH_2$、$CON(R^0)$低級アルキル、置換されていてもよい炭化水素環、置換されていてもよいヘテロ環、低級アルキレン置換されていてもよい炭化水素環、低級アルキレン置換されていてもよいヘテロ環、低級アルケニレン置換されていてもよい炭化水素環、低級アルケニレン置換されていてもよいヘテロ環、低級アルキレンR^{51}、低級アルキレンCO_2R^0、CO低級アルキル、CO(置換されていてもよい炭化水素環)、CO(置換されていてもよいヘテロ環)、CO低級アルキレン(置換されていてもよい炭化水素環)、CO低級アルキレン(置換されていてもよいヘテロ環)、CN、O低級アルキル、O(置換されていてもよい炭化水素環)、O(置換されていてもよいヘテロ環)、O低級アルキレン(置換されていてもよい炭化水素環)、O低級アルキレン(置換されていてもよいヘテロ環)、S低級アルキル、S(置換されていてもよい炭化水素環)、S(置換されていてもよいヘテロ環)、S低級アルキレン(置換されていてもよい炭化水素環)、S低級アルキレン(置換されていてもよいヘテロ環)、$N(R^0)$(置換されていてもよい炭化水素環)、$N(R^0)$(置換されていてもよいヘテロ環)、$N(R^0)$低級アルキレン(置換されていてもよい炭化水素環)、$N(R^0)$低級アルキレン(置換されていてもよいヘテロ環)、$N(R^0)CO$低級アルキル、$N(R^0)CO$(置換されていてもよい炭化水素環)、$N(R^0)CO$(置換されていてもよいヘテロ環)、$N(R^0)CO$低級アルキレン(置換されていてもよい炭化水素環)、$N(R^0)CO$低級アルキレン(置換されていてもよいヘテロ環)、$N(R^0)CO$O低級アルキル、$N(R^0)CO$O低級アルキレン(置換されていてもよい炭化水素環)、$N(R^0)CO$O低級アルキレン(置換されていてもよいヘテロ環)、CO O低級アルキレン(置換されていてもよい炭化水素環)、CO O低級アルキレン(置換されていてもよいヘテロ環)、$CON(R^0)(R^{55})$、$C(R^{53})(R^{54})R^{55}$又は低級アルキレン$C(R^{53})(R^{54})R^{55}$、である。

【0019】

「置換されていてもよい炭化水素環」又は「置換されていてもよいヘテロ環」における置換基は、好ましくは、下記G群に示す基である。

G群：(i) X C_{1-6}アルキレンA、(ii) C_{1-6}アルキレンA又は(iii) Bで示される基。

ここで、

Xは、O、S、SO、SO_2、NH、$N(C_{1-6}$アルキル)、SO_2NH、$SO_2N(C_{1-6}$アルキル)、$NHSO_2$、$N(C_{1-6}$アルキル)SO_2、CO、CO_2、O CO、CONH、$CON(C_{1-6}$アルキル)、NHCO、$N(C_{1-6}$アルキル)COまたはNHCONH、

Aは、CN、OH、CO_2H、CO_2C_{1-6}アルキル、NO_2、SO_3H、NH_2、$CONH_2$、SO_2NH_2、ハロゲンで置換されたC_{1-6}アルキル、NH C_{1-6}アルキレンO C_{1-6}アルキル、$N(C_{1-6}$アルキル)C_{1-6}アルキレンO C_{1-6}アルキル、N C_{1-6}アルキレンO C_{1-6}アルキル)$_2$、炭化水素環、ヘテロ環、X C_{1-6}アルキル、Xハロゲンで置換されたC_{1-6}アルキル、X炭化水素環、Xヘテロ環、X C_{1-6}アルキレンCN、X C_{1-6}アルキレンOH、X C_{1-6}アルキレンCO$_2$H、X C_{1-6}アルキレンCO_2C_{1-6}アルキル、X C_{1-6}アルキレンNO_2、X C_{1-6}アルキレンSO_3H、X C_{1-6}アルキレンNH_2、X C_{1-6}アルキレン$CONH_2$、X C_{1-6}アルキレンSO_2NH_2、X C_{1-6}アルキレン炭化水素環又はX C_{1-6}アルキレンヘテロ環、

BはC_{1-6}アルキル、ハロゲン、ハロゲンで置換されたC_{1-6}アルキル、又はAに記載の基であり、

上記A及びBにおける炭化水素環及びヘテロ環は、C_{1-6}アルキル、ハロゲン、ハロゲンで置換されたC_{1-6}アルキル、CN、OH、O C_{1-6}アルキル、NH_2、NH C_{1-6}アルキル、$N(C_{1-6}$アルキル)$_2$、S C_{1-6}アルキル、SO C_{1-6}アルキル、SO_2C_{1-6}アルキル、SO_2NH_2、SO_2NH C_{1-6}アルキル、$SO_2N(C_{1-6}$アルキル)$_2$、$NHSO_2$ C_{1-6}アルキル、CO_2H、CO_2C_{1-6}アルキル、$CONH_2$、CONH C_{1-6}アルキル、$CON(C_{1-6}$アルキル)$_2$及びNHCO C_{1-6}アルキルから選択される置換基を1から5個有していてもよい。

【0020】

「置換されていてもよいフェニル」における置換基は、好ましくは、上記G群に示す基

であり、更に好ましくは、C_{1-6}アルキル、OC_{1-6}アルキル又はハロゲンである。

【００２１】

本発明の一般式（Ｉ）における好ましい化合物は以下の化合物又はその製薬学的に許容される塩である：

R^1がOC_{1-6}アルキル、より好ましくはOC_{1-4}アルキル、更に好ましくはＯメチルである化合物。R^2がハロゲン、OC_{1-6}アルキル又はOC_{1-6}アルキレン 炭化水素環、より好ましくはハロゲン、OC_{1-4}アルキル又はOCH_2C_{3-8}シクロアルキル、更に好ましくはＯメチルである化合物。NR^3R^4が、$NH.CH(R^{53})R^{55}$又はN(炭化水素環)C_{1-6}アルキレン 置換されていてもよいヘテロ環)の化合物であり、ここに、R^{53}としては炭化水素環、特にフェニルが好ましく、R^{55}としては置換されていてもよいヘテロ環、特に置換されていてもよいピリジル基が好ましい。別の好ましいNR^3R^4の態様としてはピペラジン１イルで、当該ピペラジン１イルの４位が、置換されていてもよい炭化水素環又は置換されていてもよいヘテロ環で置換された化合物であり、より好ましくは当該ピペラジン１イルの４位が、置換されていてもよいフェニル又は置換されていてもよいピリジルで置換された化合物であり、ここに当該フェニル及びピリジルは、前記Ｇ群から選択される基を好ましくは１又は２個、より好ましくは１個有する。

【００２２】

本発明の一般式（Ｉ）における特に好ましい化合物は以下の化合物又はその製薬学的に許容される塩である：

1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 4 (4 メトキシフェニル)ピペラジン、N [(1 ベンジルピペリジン 4 イル)(フェニル)メチル] 6 (3.4 ジメトキシフェニル)ピリジン 2 カルボキサミド、6 (3.4 ジメトキシフェニル) N [フェニル(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド、N (1 ベンジル 4 フェニル 4 ピペリジル) 6 (3.4 ジメトキシフェニル)ピリジン 2 カルボキサミド、6 (3.4 ジメトキシフェニル) N (2 モルホリノ 1 フェノキシメチルエチル)ピリジン 2 カルボキサミド、6 (3.4 ジメトキシフェニル) N (2 モルホリノエチル) N (1.2.3.4 テトラヒドロ 1 ナフチル)ピリジン 2 カルボキサミド、trans 6 (3.4 ジメトキシフェニル) N (2 メトキシエチル) N (2 メチルスルファニルシクロペンチル)ピリジン 2 カルボキサミド、1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] N.N ジエチルデカヒドロキノリン 2 カルボキサミド、1 (4 {4 [6 (3 シクロアロピルメトキシ 4 メトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェニル)エタノン、4' {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}アセトアニリド、3 ジエチルアミノ 4' {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}プロパンアニリド、4 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェニル)モルホリン、1 [2 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェノキシ)エチル]ピペリジン 4 オール、4 (2 [(6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル) 3 ピリジル)オキシ]エチル)モルホリン、trans 5 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 2.5 ジメチルピペラジン 1 イル}フェニル)ペンタン酸及び 1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 4 {4 [(1 オキシド 4 ピリジル)メトキシ]フェニル}ピペラジン。特に、4 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェニル)モルホリンが好ましい。

【００２３】

本発明の有効成分である化合物（Ｉ）は置換基の種類によっては幾何異性体や互変異性体が存在する場合があるが、本発明にはこれらの異性体の分離したもの、あるいは混合物が包含される。

また、化合物（Ｉ）は不斉炭素原子を有する場合があり、これに基づく（Ｒ）体、（Ｓ）体の光学異性体が存在しうる。本発明はこれらの光学異性体の混合物や単離されたものを全て包含する。

更に、化合物（Ｉ）には、薬理学的に許容されるプロドラッグも含まれる。薬理学的に

許容されるプロドラッグとは、加溶媒分解により又は生理学的条件下で本発明のNH_2、OH、CO_2H等に変換できる基を有する化合物である。プロドラッグを形成する基としては、Prog. Med., 5: 2157-2161 (1985)や「医薬品の開発」（廣川書店、1990年）第7巻 分子設計163-198に記載の基が挙げられる。

【００２４】

化合物（Ｉ）は、酸付加塩又は置換基の種類によっては塩基との塩を形成する場合もある。かかる塩としては、製薬学的に許容される塩であり、具体的には、塩酸、臭化水素酸、ヨウ化水素酸、硫酸、硝酸、リン酸等の無機酸、ギ酸、酢酸、プロピオン酸、シュウ酸、マロン酸、コハク酸、フマル酸、マイレン酸、乳酸、リンゴ酸、酒石酸、クエン酸、メタンスルホン酸、エタンスルホン酸、アスパラギン酸、グルタミン酸等の有機酸との酸付加塩、ナトリウム、カリウム、マグネシウム、カルシウム、アルミニウム等の無機塩基、メチルアミン、エチルアミン、エタノールアミン、リジン、オルニチン等の有機塩基との塩やアンモニウム塩等が挙げられる。

また、本発明は、化合物（Ｉ）及びその塩の各種の水和物や溶媒和物及び結晶多形の物質を含む医薬組成物をも包含する。

【００２５】

（製造法）

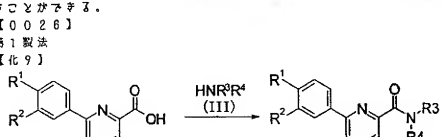
本発明の有効成分である化合物（Ｉ）及びその製薬学的に許容される塩は、その基本骨格あるいは置換基の種類に基づく特徴を利用し、種々の公知の合成法を適用して製造することができる。その際、官能基の種類によっては、当該官能基を原料乃至中間体の段階で適当な保護基で保護、又は当該官能基に容易に転化可能な基に置き換えておくことが製造技術上効果的な場合がある。このような官能基としては例えばアミノ基、水酸基、カルボキシル基等であり、それらの保護基としては例えばグリーン(T. W. Greene)及びウッツ(P. G. M. Wuts)著、「Protective Groups in Organic Synthesis（第3版、1999年）」に記載の保護基を挙げることができ、これらを反応条件に応じて適宜選択して用いればよい。このような方法では、当該保護基を導入して反応を行った後、必要に応じて保護基を除去、あるいは所望の基に転化することにより、所望の化合物を得ることができる。

また、化合物（Ｉ）のプロドラッグは上記保護基と同様、原料乃至中間体の段階で特定の基を導入、あるいは得られた化合物（Ｉ）を用い反応を行うことで製造できる。反応は通常のエステル化、アミド化、脱水等、当業者により公知の方法を適用することにより行うことができる。

【００２６】

第１製法

【化９】



(II) (I)

本製法は、カルボン酸化合物（II）よりアミド化反応により化合物（Ｉ）を製造する方法である。

【００２７】

反応は、化合物（II）を縮合剤（例えば、ジシクロヘキシルカルボジイミド（DCC）、ジイソプロピルカルボジイミド（DIPC）、１エチル３(３ジメチルアミノプロピル)カルボジイミド（WSC）、1,1'カルボニルビス 1H イミダゾール（CDI）等）、場合によっては、更に添加剤（例えば、Ｎヒドロキシスクシンイミド（HONSu）、１ヒドロキシベンゾトリアゾール（HOBt）等）の存在下、アミン化合物（III）と縮合することにより行うことができる。また、化合物（II）と上記添加剤との活性エステル体を一旦単離後、アミン

化合物（[II]）と縮合してもよい。溶媒としては、例えば、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、ジエチルエーテル、テトラヒドロフラン(THF)、1.4 ジオキサン、ジメトキシエタン等のエーテル類、ジクロロメタン、1.2 ジクロロエタン、クロロホルム等の八ロゲン化炭化水素類、N.N ジメチルホルムアミド(DMF)、N メチル 2 ピロリドン(NMP)、ピリジン等が挙げられる。これらの溶媒は単独で、又は 2 種以上混合して用いられる。

【0028】

第2製法

一般式（I）における基R^2又はR^1上に種々の置換基を有する化合物、或いはR^1若しくはR^2がアルコキシ基以外の基である化合物は、化合物（I）を原料として、当業者にとって自明である反応、又はこれらの変法を用いることにより、容易に合成することができる。例えば以下の反応が適用できる。

（1）求核置換反応によるアルキル化

O、S 又はN アルキル化反応は、OH、SH又は一級乃至三級アミノ基を有する化合物と、アルキルクロリド等のアルキル八ライド又は有機スルホン酸エステル等のアルキル化剤とを反応させることで製造できる。あるいは、光延反応に付すことによっても製造できる。芳香族炭化水素類、エーテル類、アルコール類（メタノール、エタノール等）、DMF、NMP、ジメチルスルホキシド(DMSO)等の反応に不活性な有機溶媒中、当量あるいは一方を過剰量用いて、冷却下～加熱下に行われる。水素化ナトリウム、水素化カリウム、リチウムジイソプロピルアミド、リチウムヘキサメチルジシラジド、ナトリウムメトキシド、カリウム tert ブトキシド、水酸化ナトリウム、水酸化カリウム、炭酸ナトリウム、炭酸カリウム等の塩基の存在下に反応させるのが、反応を円滑に進行させる上で有利な場合がある。

（2）還元的アルキル化

一級若しくは二級アミンを有する化合物と、ケトンやアルデヒド等のカルボニル化合物とを反応させることにより、アルキル化を行うことができる。反応は還元的アルキル化（カルボニル化合物から見れば還元的アミノ化）の常法を用いることができ、例えば日本化学会編「実験化学講座(第4版)」20巻（1992年）(丸善)等に記載の方法が挙げられる。

【0029】

（3）アミド化、スルホンアミド化及びエステル化

カルボン酸若しくはスルホン酸化合物を用い、前記第1製法の縮合剤を使用する方法又はそれらの反応性誘導体を使用する方法により製造できる。カルボン酸若しくはスルホン酸化合物の反応性誘導体としては、酸八ライド、酸無水物、活性エステル等が使用できる。反応は、例えば日本化学会編「実験化学講座(第4版)」22巻（1992年）（丸善）等に記載の方法により行うことができる。

（4）加水分解

カルボン酸エステル体を加水分解することによって、カルボキシル基を有する本発明化合物を製造できる。反応は加水分解の常法を用いることができ、例えば、前述の「Protective Groups in Organic Synthesis（第3版）」のカルボキシル基の脱保護反応等に記載の方法を適用することができる。

【0030】

（5）酸化

ピリジン N オキシド等のオキシド化合物はピリジンやアミノ基等を有する化合物を酸化することにより製造できる。酸化剤としては、過酸化水素、Oxone（商品名、Aldrich）、過ホウ酸ナトリウム等の無機酸化剤や過酢酸、m クロロ過安息香酸、ジメチルジオキシラン等の有機酸化剤を用いることが出来る。反応は八ロゲン化炭化水素類、芳香族炭化水素類、エーテル類、DMF、酢酸、水等の反応に不活性な溶媒中または無溶媒下、冷却下～加熱下に行われる。反応に際しては、原料化合物に対し酸化剤を当量若しくは過剰に用いることができ、無機酸（好ましくは、硫酸、硝酸、塩酸、臭化水素酸）、有機酸（好ましくは、酢酸、トリフルオロ酢酸）、無機塩基（好ましくは、水酸化ナトリウム、水酸化カリウム、炭酸水素ナトリウム）の存在下に反応させるのが、反応を円滑に進行させる上で

有利な場合がある。また、スルフィニル又はスルホニル化合物はスルファニル化合物を用い、同様の酸化反応に付すことにより製造できる。

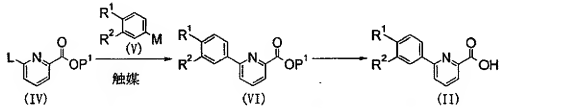
（６）接触還元

OH基を有する本発明化合物は、Oベンジル基を有する化合物を脱ベンジル化反応に付すことにより製造できる。例えば、水素雰囲気下、パラジウム炭素触媒の存在下に反応を行う接触還元の常法を用いることができ、前述の「Protective Groups in Organic Synthesis（第３版）」のOH基の脱保護反応等に記載の方法を適用することもできる。また、同様の接触還元の方法により、アルケニル基をアルキル基に変換することができる。

【００３１】

原料合成

【化１０】



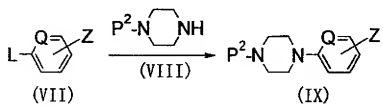
（式中、Lは脱離基を、P^1はカルボキシル基の保護基を、Mは金属をそれぞれ示す。以下同様。）

カルボン酸化合物（II）は化合物（VI）を加水分解することにより製造できる。保護基P^1は前述の「Protective Groups in Organic Synthesis（第３版）」のカルボキシル基の保護基を適用でき、同文献に記載の脱保護反応や加水分解の常法等により除去することができる。

原料化合物（VI）はピリジン誘導体（IV）とアリール金属化合物（V）を触媒存在下にカップリングさせることにより製造できる。反応は、Comprehensive Organic Synthesis. Volume 3. 481. 1991等に記載の方法が適用できる。脱離基Lとしては八ロゲン、トリフルオロメタンスルホニルオキシ等が、金属Mとしては、例えばヒドロキシホウ素、アルキルホウ素、アルコキシホウ素、八ロゲン化マグネシウム、八ロゲン化亞鉛、アルキルズズ、アルキル錫等が挙げられる。触媒としては、テトラキストリフェニルホスフィンパラジウム、酢酸パラジウム等のパラジウム錯体、或いはジクロロビス（トリフェニルホスフィン）ニッケル、ビス（1.5 シクロオクタジエン）ニッケル等のニッケル錯体が好ましい。反応は、八ロゲン化炭化水素類、エーテル類、芳香族炭化水素類、DMF、水等の反応に不活性な溶媒中又は無溶媒下、冷却下～加熱下に行われる。反応に際しては、化合物（IV）とアリール金属化合物（V）を当量若しくは一方を過剰に用いることができ、トリエチルアミン、ピリジン、4（N.N ジメチルアミノ）ピリジン、水酸化ナトリウム、炭酸ナトリウム、水素化ナトリウム、メトキシナトリウム又はtert アトキシカリウム等の塩基の存在下に反応させるのが、反応を円滑に進行させる上で有利な場合がある。

【００３２】

【化１１】



（式中、QはCH又はNを、P^2はH又はアミノ基の保護基を、ZはG群より選択される基等をそれぞれ示す。）

原料化合物（IX）は、アリール誘導体（VII）を保護されていてもよいピペラジンとの

カップリング反応又はイアソ置換反応に付すことによって合成できる。カップリング反応は前記原料化合物（VI）の製造法に記載の方法が適用できる。イアソ置換反応は前記（1）求核置換反応によるアルキル化の条件が適用できる。保護基P^2は前述の「Protective Groups in Organic Synthesis（第3版）」のアミノ基の保護基を適用でき、反応後、原料化合物（IX）を同文献に記載の脱保護反応により、除去することができる。

【0033】

上記各製法により得られた反応生成物は、遊離化合物、その塩あるいは水和物など各種の溶媒和物として単離され、精製される。塩は通常の造塩処理に付すことにより製造できる。

単離、精製は、抽出、濃縮、留去、結晶化、　過、再結晶、各種クロマトグラフィー等通常の化学操作を適用して行われる。

各種異性体は異性体間の物理化学的な差を利用して常法により単離できる。例えば、光学異性体は一般的な光学分割法、例えば分別結晶化又はクロマトグラフィー等により分離できる。また、光学異性体は、適当な光学活性な原料化合物より製造することもできる。

【0034】

更に、本発明は、4（4（4［6（3,4ジメトキシフェニル）ピリジン2カルボニル］ピペラジン1イル）フェニル）モルホリン（化合物A）の結晶にも関する。本発明の結晶は、医薬の製造原体として使用可能な程度に安定な結晶であればよく、特に下記物性値を有するα型又はβ型の結晶が好ましい。各結晶はそれぞれ下記の粉末X線回折スペクトル［2θ（°）］で特徴付けられる。尚、粉末X線回折はデータの性質上、結晶の同一性認定においては、結晶格子間隔や全体的なパターンが重要であり、相対強度は結晶成長の方向、粒子の大きさ、測定条件によって多少変わりうるものであるから、厳密に解釈されるべきではない。

α型：10.82、12.86、16.96、19.90、21.76及び22.88。

β型：11.66、14.92、16.92、19.44、20.10、21.06及び21.90。

また、DSC分析で、α型結晶は138～142℃に、β型結晶品は126～130℃にそれぞれ熱吸収ピーク（補外開始温度（オンセット））を有する。

【0035】

α型及びβ型いずれの結晶も40℃相対湿度75%下、或いは80℃下においても2ヶ月間は安定であり、医薬の製造原体として使用可能であり、特に固形製剤の原体として好適である。α型結晶品は酢酸エチルより再結晶を行うことにより晶出し易く、同条件でα型結晶とβ型結晶品の結晶混合物を生じることもある。また、α型結晶品の種結晶を使用して、酢酸エチル－エタノール混合溶媒より再結晶を行うことにより、再現性良くα型結晶を得ることができる。一方、β型結晶品は、α型結晶品とβ型結晶品の結晶混合物を、酢酸エチル、メタノール、エタノール、アセトン等の溶媒、或いはそれらの混合溶媒（好ましくは、酢酸エチル－エタノール、アセトン－エタノール又はアセトン－メタノール）に懸濁させ、　することにより得ることができる。また、β型結晶品の種結晶を使用して、上記混合溶媒より再結晶を行うことにより、再現性良くβ型結晶品を得ることができる。β型結晶品は、溶媒の種類を変えても析出しやすいこと、α型結晶品が混在していても懸濁下の　処理によりβ型結晶品へ変換可能であることから、工業的生産における大スケールでの製造にも好適である。本発明は、α型結晶、β型結晶品及びそれらを含有する混合物をも包含する。

【0036】

化合物（I）又はその塩の1種又は2種以上を有効成分として含有する製剤は通常製剤化に用いられる担体や賦形剤、その他の添加剤を用いて調製される。

投与は錠剤、丸剤、カプセル剤、　粗剤、散剤、液剤等による経口投与、あるいは静注、筋注等の注射剤、坐剤、経皮剤、経鼻剤あるいは吸入剤等による非経口投与のいずれの形態であってもよい。投与量は症状、投与対象の年齢、性別等を考慮して個々の場合に応じて適宜決定されるが、通常、経口投与の場合、成人1日当たり0.001 mg/kg乃至100 mg/kg程度であり、これを1回で、あるいは2～4回に分けて投与する。また、症状によって静脈投与される場合は、通常、成人1回当たり0.0001 mg/kg乃至10 mg/kgの範囲で1日に

1回乃至複数回投与される。また、吸入の場合は、通常、成人1回当たり0.0001 mg/kg乃至1 mg/kgの範囲で1日に1回乃至複数回投与される。

本発明による経口投与のための固体組成物としては、錠剤、散剤、　粗剤等が用いられる。このような固体組成物においては、一つ又はそれ以上の活性物質が、少なくとも一つの不活性な賦形剤、例えば乳糖、マンニトール、ブドウ糖、ヒドロキシプロピルセルロース、微結晶セルロース、デンプン、ポリビニルピロリドン、メタケイ酸アルミン酸マグネシウム等と混合される。組成物は、常法に従って、不活性な添加剤、例えばステアリン酸マグネシウム等の滑沢剤やカルボキシメチルスターチナトリウム等の崩壊剤、溶解補助剤を含有していてもよい。錠剤又は丸剤は必要により糖衣又は胃溶性若しくは腸溶性コーティング剤で被覆してもよい。

【００３７】

経口投与のための液体組成物は、薬剤的に許容される乳剤、液剤、懸濁剤、シロップ剤、エリキシル剤等を含み、一般的に用いられる不活性な溶剤、例えば精製水、エタノールを含む。この組成物は不活性な溶剤以外に可溶化剤、湿潤剤、懸濁化剤のような補助剤、甘味剤、矯味剤、芳香剤、防腐剤を含有していてもよい。

非経口投与のための注射剤としては、無菌の水性又は非水性の液剤、懸濁剤、乳剤を含む。水性の溶剤としては、例えば注射用蒸留水及び生理食塩水が含まれる。非水性の溶剤としては、例えばプロピレングリコール、ポリエチレングリコール、オリーブ油のような植物油、エタノールのようなアルコール類、ポリソルベート80（商品名）等がある。このような組成物は、さらに等張化剤、防腐剤、湿潤剤、乳化剤、分散剤、安定化剤、溶解補助剤を含んでもよい。これらは例えばバクテリア保留フィルターを通す　過、殺菌剤の配合又は照射によって無菌化される。また、これらは無菌の固体組成物を製造し、使用前に無菌水又は無菌の注射用溶媒に溶解、懸濁して使用することもできる。

吸入剤や経鼻剤等の経粘膜剤は固体、液体、半固体状のものが用いられ、従来公知の方法に従って製造することができる。例えば、ラクトースや澱粉のような賦形剤や、更に、pH調整剤、防腐剤、界面活性剤、滑沢剤、安定剤や増粘剤等が適宜添加されていてもよい。投与は、適当な吸入又は吹送のためのデバイスを使用することができる。例えば、計量投与吸入デバイス等の公知のデバイスや噴霧器を使用して、化合物を単独で又は処方された混合物の粉末として、もしくは医薬的に許容し得る担体と組み合わせて溶液又は懸濁液として投与することができる。乾燥粉末吸入器等は、単回又は多数回の投与用のものであってもよく、乾燥粉末又は粉末含有カプセルを利用することができる。あるいは、適当な駆出剤、例えば、クロロフルオロアルカン、ヒドロフルオロアルカン又はニ酸化炭素等の好適な気体を使用した加圧エアゾールスプレー等の形態であってもよい。

【００３８】

また、本発明のピリジン誘導体又はその製薬学的に許容される塩を有効成分として含有する医薬組成物は、治療上有効な他の有効成分、例えば、ホルモテロール等のβ２アゴニスト、ステロイド剤、抗コリン剤、ロイコトリエン　拮抗剤、リポキシゲナーゼ阻害剤、サイトカイン阻害剤等と適宜組み合わせて、併用してもよい。これらと併用する場合は、同時に投与するための配合剤として、あるいは順次に投与するために組み合わされた別個の製剤として使用してもよい。

【実施例】

【００３９】

以下、実施例によって本発明を具体的に説明するが、これらは本発明の範囲を限定するものではない。また、本発明の医薬の有効成分であるフェニルピリジン誘導体の製法を製造例に、当該化合物の原料化合物の製法を参考例に示す。

実施例１（PDE4阻害活性）

１）PDE4を含有する溶液は、以下の通りラット心室筋より精製した。雄性ウイスターラットよりエーテル麻酔下で摘出した心臓を生理食塩水で洗浄後、心室を分離した。分離した心室をはさみで細かく切断し、これを1%PROTEASE INHIBITOR COCKTAIL For Mammalian Cell Extracts (SIGMA)を含む緩衝液A（20 mM Bis Tris, 50 mM 酢酸ナトリウム、2 mM E

DTA、5 mM 2 メルカプトエタノール、2 mM benzamidene、0.05 mM phenyl methyl sulfonyl fluoride、pH 6.5)に懸濁後、ポリトロンにより細胞を破壊し、超遠心(100.000 G、60分間、4℃)することにより可溶性画分を得た。

2)緩衝液Aで平衡化された2.6×10 cm Qセファロースカラムに、得られた可溶性画分を充填した。ついで該カラムを緩衝液A 1200 mlで洗浄し未結合蛋白を除去した。該カラムに結合した蛋白を0.05～1.00 M酢酸ナトリウムの線形勾配液を含有する緩衝液A 750 mlを用いて溶出し、7 ml分画110本を回収した。cGMP及びカルシウム/カルモジュリン存在または非存在下で得られた各分画のcAMP代謝PDE活性について検査した。各分画中のcAMPの代謝活性を有しかつcGMP又はカルシウム/カルモジュリンの存在によりcAMP代謝活性が影響を受けない分画をPDE4阻害活性を検査するための貯蔵溶液として使用した。

3)試験化合物は所望の濃度を40 mM Tris HCl(pH 8.0)、5 mM 塩化マグネシウム、4 mM 2 メルカプトエタノール、1 μM cAMP、1 μCi/ml [^{3}H]cAMP及びPDE4貯蔵溶液の含有している反応混合液中で30℃で10分間反応させた。反応液に羊蟹の18 mM 硫酸亜鉛、5 μM 3 ISOBUTYL 1 METHYLXANTHINE(IBMX)を含む20 mg/ml Polylysine coated yttrium silicate SPA beads(Amersham)懸濁液を加え反応を停止させ、放射活性を測定した。

IC_{50}はPDE4の代謝活性を50%阻害する試験化合物濃度として、各化合物について算出した。

上記試験法とWO97/19078公報に記載の方法を応用して、PDE1、PDE2、PDE3及びPDE5阻害活性を同様に測定した。

上記測定の結果、化合物(I)はPDE4に対し良好な阻害活性を示し、中でも後記製造例2、4、5、36、48、57、75、82、96、99、137、164、171、180、191、199及び210の化合物は、IC_{50}が12 nM以下という強力な活性を示した。また、同濃度ではPDE1、PDE2、PDE3及びPDE5に対し阻害活性をほとんど示さなかった。従って、化合物(I)は選択的かつ優れたPDE4阻害剤であることが確認された。

【0040】

実施例2(TNF α産生阻害活性を指標とした経口吸収性評価試験)

1)8週齢雄性フィッシャーラットに、0.5%メチルセルロース精製水に懸濁した試験化合物10 mg/kgを経口投与した。また対照群には、溶媒(0.5%メチルセルロース精製水、3 ml/kg)を同様に投与した。経口投与後、経時的にエーテル麻酔を施したラットの尾静脈よりヘパリン存在下で採血を行い、常法に従って血　を調製した。

2)96穴培養プレートに1穴あたりの全量が200 μlとなるように、上で調製した血　(最終濃度2.5%)、10%牛胎児血清を含むRPMI1640培地、雄性ウイスターラットの全血20 μl及びLPS(最終濃度3 μg/ml)を分注し、CO_2インキュベーターを用いて37℃で一晩培養した。培養終了後、プレートを遠心(1500 r.p.m.、10分間)し、上清を回収し、市販のELISA kitを用いて上清中のTNF α量を測定した。

上記試験の結果、製造例化合物は良好な経口吸収性を有することが判明した。

上記阻害活性測定試験の結果、化合物(I)はPDE4に対し選択的で強力な阻害活性を示すことが確認され、また経口吸収性も良好であることから、PDE4の関与する疾患の予防・治療薬として有用である事が明らかである。

【0041】

実施例3(抗原誘発ラット気道内好酸球浸潤に対する作用)

4週齢のBrown Norway系雄性ラット(日本チャールスリバー、神奈川)に感作用OA溶液(最終濃度:OA:1 mg/ml、$Al(OH)_3$:20 mg/ml)を、3日間連続して1匹当たり1 ml腹腔内投与することにより抗原感作を行った。なお、投与初日をDay 0とした。Day 21又は22に1%OA/生理食塩液を超音波ネブライザー(NE U12、オムロン)で霧化し、感作ラットに20分間吸入させることで抗原暴露し、気道内への好酸球の浸潤を惹起した。また、生理食塩液を吸入暴露した群を正常対照群として用いた。試験化合物を0.5%MC水溶液に懸濁し、抗原吸入暴露開始の1時間前に経口投与した。なお動物は、抗原吸入暴露の前日より絶食とし、抗原吸入暴露後に絶食を解除した。抗原吸入暴露から24時間後、動物をネンブタール麻酔下に開腹し腹部大動脈より放血致死させた後、気管にカニューレ(6 Fr アトム静脈カテーテ

ル、アトム)を挿入し2 mlのヘパリン(1 unit/ml)含有生理食塩液を注入・回収する操作を5回(計10 ml)繰り返すことにより、気管支肺胞洗浄(BAL：Bronchoalveolar Lavage)を行った。回収したBAL液を500x9 (4℃、10分間)で遠心後、上清を除去し、その沈 (細胞画分)を500μlのヘパリン(1 unit/ml)含有生理食塩液で再懸濁した。再懸濁液の総白血球濃度を血球計数装置(Celltac α、日本光電)で測定した後、塗沫標本を作製し鑑別用血液染色液(ディフ・クイック、国際試薬)で染色後、顕微鏡下で観察し、形態的特徴から好酸球の存在比率を算出した。総白血球数及び好酸球存在比率より、好酸球数の総数を算出し、薬物の効果を評価した。

上記測定の結果、製造例2、36及び180の化合物は、3.0 m9/kgの経口投与において、それぞれ60%、92%、31%の阻害活性を示した。なお、本試験において製造例36の化合物(化合物A)はα型結晶を使用したが、α型結晶とβ型結晶は、水、pH1.2又はpH6.8緩衝液に対し、ほぼ同等の溶解度を有することから、β型結晶も同様に有効であると考えられる。

【0042】

実施例4 (ラットLPS誘発気道内好中球浸潤に対する作用)

過量のケタミン/キシラジン混合液を腹腔内投与することにより麻酔を施した6週齢のWistar系雄性ラット(日本チャールスリバー、神奈川)に、生理食塩液に溶解した10μg/mlのLPS (Lipopolysaccharide E.coli 0127:B8 Bolvin, DIFCO)溶液を200μlソンデを用いて気道内投与することで気道内への好中球の浸潤を惹起した。また、生理食塩液を気道内投与した群を正常対照群として用いた。試験化合物を0.5%MC水溶液に懸濁し、LPS気道内投与の1時間前に経口投与した。なお動物は、LPS気道内投与の前日より絶食とし、LPS気道内投与後に絶食を解除した。LPS気道内投与から24時間後、動物をネンブタール麻酔下に開腹し腹部大動脈より放血致死させた後、以下上記実施例3と同様にして総白血球濃度を測定した。更に同様にして、顕微鏡下で観察した形態的特徴から好中球の存在比率を算出した。総白血球数及び好中球存在比率より、好中球数の総数を算出し、薬物の効果を評価した。

【0043】

参考例及び後記表中以下の略号を用いる。Ex：製造例番号、Dat：物理化学的データ(F：FAB MS(M+H)$^+$、FN：FAB MS(M H)、EI：EI MS(M$^+$)、AP：APCI MS(M+H)$^+$、MP：融点(℃)、NMR1：$CDCl_3$中の^{1}H NMRにおける特徴的なピークのδ(ppm)、NMR2：DMSO d_6中の^{1}H NMRにおける特徴的なピークのδ(ppm)、RT：HPLC(Wakosil II 5C18AR 2.0 x 30 mm. 5 mM TFAaq / MeOH = 9/1(0 min) 0/10(7.5 min) 0/10(8 min). 1.2 ml/min. 35℃. 254 nm)における保持時間(min))、Sal：塩及び含有溶媒(Ox：シュウ酸塩、Fum：フマル酸塩、空欄：フリー体、成分の前の数字は例えば2 HClは2塩酸塩を示す)、Syn：製造法(数字は同様に製造した製造例番号を示す)、Me：メチル、Et：エチル、iPr：2プロピル、cPr：シクロプロピル、tBu：tブチル、cHex：シクロヘキシル、Ph：フェニル、Bn：ベンジル、Ac：アセチル、Pip：ピペリジン1イル、Pip4：ピペリジン4イル、Pipr：ピペラジン1イル、Pyrr：ピロリジン1イル、4 Me Pipr：4メチルピペラジン1イル。また、置換基の前の数字は置換位置を示し、例えば2 Clは2クロロを、3.4 diMeは3.4ジメチルを、2.3.4 triMeは2.3.4トリメチルを、3.4 (OCH_2O)は3.4メチレンジオキシ基をそれぞれ表す。

粉末X線回折の測定には、MAC Science MXP18TAHF22を用い、管球：Cu、管電流：120 mA、管電圧：50 kV、サンプリング幅：0.020°、走査速度：8° /min、波長：1.54056Å、測定回折角範囲(2θ)：5~40°の条件で測定した。

熱分析(DSC及びTGA)はそれぞれ次の条件で測定した。

DSC：TA Instrument TA 5000、室温~400℃ (10℃/min)、N2 (50 ml/min)、アルミニウム製サンプルパン。TGA：TA Instrument TA 5000、室温~400℃ (10℃/min)、N2 (100 ml/min)、白金製サンプルパン。

【0044】

参考例1

6 クロロピリジン 2 カルボン酸メチル、3.4 ジメトキシフェニルホウ酸、ジメトキシエタン及び水の混合物に酢酸パラジウム、トリフェニルホスフィン及び炭酸ナトリウムを加え100℃で1時間反応して、6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸メチルを得た。得られた化合物をTHF メタノール混合溶液中、1M水酸化ナトリウム水溶液を加え60℃で加熱下30分間反応して、6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸を得た。NMR2: 8.18 (1H. d. J=8.0 Hz). 7.09 (1H. d. J=8.0 Hz). 3.87 (3H. s) : F: 260。

参考例 2

4 ベンゾイル安息香酸メチルのピリジン溶液に、ヒドロキシルアミン塩酸塩を加え加熱下反応させて得た4 メトキシカルボニルベンゾフェノンオキシムを、メタノール中、パラジウム炭素存在下、水素雰囲気下反応させて、4 (α アミノベンジル)安息香酸メチルを得た。F: 242。

参考例 3

4 ブロモ 2 クロロアニソールのTHF溶液に 78℃で、n ブチルリチウム／n ヘキサン溶液を加え、30分 した。次いで、ホウ酸トリメチルを加え室温まで昇温し30分 した。溶媒を留去して得られた残 を3.4 ジメトキシフェニルホウ酸の代わりに用い、参考例1と同様にして、6 (3 クロロ 4 メトキシフェニル)ピリジン 2 カルボン酸を得た。FN: 262。

【0045】

参考例 4

参考例3と同様にして、6 (3 フルオロ 4 メトキシフェニル)ピリジン 2 カルボン酸を製造した。FN: 246。

参考例 5

参考例3と同様にして、6 (3 ベンジルオキシ 4 メトキシフェニル)ピリジン 2 カルボン酸を製造した。NMR1: 6.95 7.05(1H. m). 5.28(2H. s). 3.95(3H. s)。

参考例 6

1 ベンジルオキシ 4 ブロモ 2 メトキシベンゼンを用い、参考例3と同様に（但し、加水分解は1M水酸化ナトリウム水溶液中、100℃で2.5日間行った）して、6 (4 ベンジルオキシ 3 メトキシフェニル)ピリジン 2 カルボン酸を製造した。F: 338。

参考例 7

N.N ジエチルキノリン 2 カルボキサミドのエタノール溶液に濃塩酸、酸化白金を加え、3気圧の水素雰囲気下3日間反応させて、N.N ジエチルデカヒドロキノリン 2 カルボキサミドを得た。F: 239。

参考例 8

6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸とt ブトキシカルボニルピペラジンを用い、後述の製造例2と同様の方法により1 {[6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 4 (t ブトキシカルボニル)ピペラジンを得、更に、4M塩化水素／酢酸エチル溶液を加え反応して、1 {[6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジンを得た。F: 328。

【0046】

参考例 9

1 アミノ 1.2.3.4 テトラヒドロナフタレンのアセトニトリル溶液に氷冷下ピリジン及び塩化クロロアセチルを加え反応させ、2 クロロ N (1.2.3.4 テトラヒドロナフタレン 1 イル)アセトアミドを得た。得られた化合物のアセトニトリル溶液に、炭酸セシウム及びモルホリンを加え、室温で17時間 して、2 (モルホリン 4 イル) N (1.2.3.4 テトラヒドロナフタレン 1 イル)アセトアミドを得た。更に、得られた化合物のTHF溶液に、氷冷下、水素化リチウムアルミニウムを加え、30分間加熱還流して、N [2 (モルホリン 4 イル)エチル] 1.2.3.4 テトラヒドロナフタレン 1 イルアミンを二塩酸塩として得た。F: 261。

参考例 10

2 ブロモトルエンのトルエン溶液に、1 (t ブトキシカルボニル) 1.4 ジアゼパン、ト

リス(ジベンジリデンアセトン)ジパラジウム(0)、2.2' ビス(ジフェニルホスフィノ) 1.1' ビナフチル及びナトリウムｔ アトキシドを加え、油浴温度80℃で15時間　して、1 (ｔ アチルオキシカルボニル) 4 (2 メチルフェニル) 1.4 ジアゼパンを得た。得られた化合物のメタノール溶液に、4M塩化水素／酢酸エチル溶液を加え、室温で4時間　して、1 (2 メチルフェニル) 1.4 ジアゼパンを二塩酸塩として得た。F: 191.

参考例１１

1 (エトキシカルボニル)ピペリジン 4 オンの酢酸溶液に、3 クロロアニリン、水素化トリアセトキシホウ素ナトリウムを加え、室温で30分間　して、4 (3 クロロフェニルアミノ) 1 (エトキシカルボニル)ピペリジン塩酸塩を得た。得られた化合物に濃塩酸を加え、油浴温度100℃で2日間　して、4 (3 クロロフェニルアミノ)ピペリジン二塩酸塩を得た。F: 211.

【００４７】

参考例１２

リチウムジイソプロピルアミドのTHF溶液に、 78℃で1 ベンジル4 イソニペコチン酸エチルを加え、 78℃で1時間　した。反応液にヨウ化メチルを加え、 78℃で30分間　し、更に徐々に室温に昇温しながら1時間　して、1 ベンジル 4 メチル4 イソニペコチン酸エチルを得た。得られた化合物を3M塩酸水溶液中、油浴温度100℃で3.5日間　して、1 ベンジル 4 メチル4 イソニペコチン酸塩酸塩を得た。次いで、得られた化合物をトルエン中、アジ化ジフェニルホスホリル及びトリエチルアミンを加え、30分間加熱還流した。反応液に2 (トリメチルシリル)エタノールを加え、油浴温度110℃で14時間　して、N [2 (トリメチルシリル)エトキシカルボニル] 1 ベンジル 4 メチル 4 ピペリジルアミンを得た。F: 349.

参考例１３

1 ベンジルオキシカルボニル 4 (ｔ アトキシカルボニル) ピペラジン 2 カルボン酸とモルホリンを用い、後述の製造例５と同様の方法により、1 ベンジルオキシカルボニル 4 (ｔ アトキシカルボニル) 2 [(モルホリン 4 イル)カルボニル]ピペラジンを得、酢酸エチル中、4M塩化水素／酢酸エチル溶液を加え反応させて、1 ベンジルオキシカルボニル 2 [(モルホリン 4 イル)カルボニル]ピペラジンを得た。この化合物をトルエン中、プロモベンゼン、トリス(ジベンジリデンアセトン)ジパラジウム(0)、2.2' ビス(ジフェニルホスフィノ) 1.1' ビナフチル及びナトリウムｔ アトキシド存在下、1日間加熱還流して、1 ベンジルオキシカルボニル 2 モルホリノカルボニル 4 フェニルピペラジンを得た。更に、得られた化合物をエタノール中、10%パラジウム炭素存在下、常圧の水素雰囲気下、室温で1.5日間　した。不溶物を　去後、溶媒を留去して得られた残　をエタノールに溶解し、10%パラジウム炭素及び半酸アンモニウムを加え、油浴温度70℃で2.5日間　して、2 [(モルホリン 4 イル)カルボニル] 4 フェニルピペラジンを得た。F: 276.

【００４８】

参考例１４

3 (ｔ アトキシカルボニル)アミノ 3 フェニルプロパン酸のTHF溶液にCDIを加え、油浴温度60℃で3時間　した。反応液を室温まで冷却後、モルホリンを加え、室温で1日間して、N (ｔ アトキシカルボニル) 2 [(モルホリン 4 イル)カルボニル]1 フェニルエチルアミンを得た。得られた化合物を、4M塩化水素／酢酸エチル溶液中、室温で45分間して、2 [(モルホリン 4 イル)カルボニル] 1 フェニルエチルアミンを得た。F: 235.

参考例１５

1 ベンゾイルイソニペコチン酸エチル及びプロモ酢酸エチルを用い、参考例１２に記載のアルキル化反応と同様にして得た1 ベンゾイル 4 (エトキシカルボニルメチル)イソニペコチン酸エチルを、エタノール及び1M水酸化ナトリウム水溶液中、室温で2時間、更に80℃で18時間反応させ、1 ベンゾイル 4 (カルボキシメチル)イソニペコチン酸を得た。この化合物にトリフルオロ酢酸無水物を加え、室温で30分間　した。溶媒を留去して得られた残　をTHFに溶解し、モルホリンを加え、室温で30分間　し、1 ベンゾイル 4 [(モルホリン 4 イル)カルボニルメチル]イソニペコチン酸を得た。更に2 (トリメチルシリル

)エタノールの代わりにベンジルアルコール用い、参考例１２に記載のエステル化反応と同様の方法で、１ベンゾイル Ｎ（ベンジルオキシカルボニル）４［（モルホリン ４ イル）カルボニルメチル］４ピペリジルアミンを得た。Ｆ：４６６。

【００４９】

参考例１６

４アロモ ２ エチルフェノールのＤＭＦ溶液に、炭酸カリウム、臭化ベンジルを加え、油浴温度６０℃で３０分間　して、ベンジル（４ アロモ ２ エチルフェニル）エーテルを得、次いで参考例３の前半部分と同様に処理して、６（４ ベンジルオキシ ３ エチルフェニル）ピリジン ２ カルボン酸メチルを得た。得られた化合物のメタノール及びＴＨＦの混合溶液中、１０％パラジウム炭素存在下、常圧の水素雰囲気下、室温で２４時間　して得られた生成物をトリフルオロ酢酸に溶解し、氷冷下ペンタメチルベンゼンを加え、油浴温度５０℃で１時間、更に室温で４．５時間　し、６（３ エチル ４ ヒドロキシフェニル）ピリジン ２ カルボン酸メチルを得た。得られた化合物をピリジン中、トリフルオロメタンスルホン酸無水物で処理し、６（３ エチル ４ トリフルオロメタンスルホニルオキシフェニル）ピリジン ２ カルボン酸メチルを得た。

更に、上記で得られた化合物の１．４ ジオキサン溶液に、トリアチルビニルスズ、塩化リチウム、テトラキス（トリフェニルホスフィン）パラジウム（０）、２．６ ジ ｔ ブチル ４ メチルフェノールを加え、１８時間加熱還流した後、更にテトラキス（トリフェニルホスフィン）パラジウム（０）を加え、２日間加熱還流した。次いで室温下、フッ化カリウムを加え、室温で２日間　し、６（３ エチル ４ ビニルフェニル）ピリジン ２ カルボン酸メチルを得た。この化合物をメタノール中、１Ｎ 水酸化ナトリウム水溶液で処理し、６（３ エチル ４ ビニルフェニル）ピリジン ２ カルボン酸とし、更に１ アミノインダンを用い、後述の製造例５と同様の方法により、６（３ エチル ４ ビニルフェニル）Ｎ インダン １ イルピリジン ２ カルボキサミドを得た。Ｆ：３８９。

【００５０】

参考例１７

６（３ エチル ４ ヒドロキシフェニル）ピリジン ２ カルボン酸メチルのＤＭＦ溶液に、炭酸カリウム、ヨウ化メチルを加え、油浴温度７０℃で２時間　し、６（３ エチル ４ メトキシフェニル）ピリジン ２ カルボン酸メチルを得、次いでメタノール及び１Ｍ水酸化ナトリウム水溶液中、油浴温度６０℃で１時間　して、６（３ エチル ４ メトキシフェニル）ピリジン ２ カルボン酸を得た。Ｆ：２５８。

参考例１８

チアゾールをＴＨＦ中、ｎ ブチルリチウム／ｎ ヘキサン溶液及びベンズアルデヒドで順次処理して得たフェニル（チアゾール ２ イル）メタノールを、トルエン ジオキサン混合溶媒中、二酸化マンガンと加熱下反応させ、フェニル（チアゾール ２ イル）ケトンを得た。次いで、ピリジン中、ヒドロキシルアミン塩酸塩と加熱下反応させ、フェニル（チアゾール ２ イル）ケトン オキシムを得た。更に、得られた化合物をエタノール 水混合溶媒中、アンモニア水及び亜鉛粉を加え加熱下反応させて、フェニル（チアゾール ２ イル）メチルアミンを得た。ＥＩ：１９０。

参考例１９

６ クロロピリジン ２ カルボン酸メチル、４ メトキシフェニルホウ酸、炭酸ナトリウム、テトラキス（トリフェニルフォスフィノ）パラジウム、ジメトキシエタン及び水の混合物を加熱下反応させ、６（４ メトキシフェニル）ピリジン ２ カルボン酸メチルを得た。得られた化合物を、無水酢酸中、発煙硝酸と反応させ、６（４ メトキシ ３ ニトロフェニル）ピリジン ２ カルボン酸メチルを得た。更に、ＴＨＦ、メタノール及び１Ｍ水酸化ナトリウム水溶液の混合溶媒中反応させて、６（４ メトキシ ３ ニトロフェニル）ピリジン ２ カルボン酸を得た。

【００５１】

参考例２０

２ アロモフェノールのアセトン溶液に臭化ベンジル及び炭酸カリウムを加え加熱下

し、2 ベンジルオキシアロモベンゼンを得た。得られた化合物をTHF中、少量のジアロモエタン存在下でマグネシウム片と処理し、次いでピリジン 4 カルボキシアルデヒドと反応させ、(2 ベンジルオキシフェニル)(ピリジン 4 イル)メタノールを得た。以下、参考例１８と同様にして、(2 ベンジルオキシフェニル)(ピリジン 4 イル)メチルアミンを得た。F: 291。

参考例２１

4 ヨードフェノールをDMF中、炭酸カリウムの存在下、2 塩化ジメチルアミノエタン塩酸塩と加熱下反応させ、[2 (4 ヨードフェノキシ)エチル]ジメチルアミンを得た。得られた化合物を、ピペラジン 1 カルボン酸 t ブチルエステル、ナトリウム t ブトキシド、トリ(2 メチルフェニル)ホスフィン及び触媒量のトリス(ジベンジリデンアセトン)ジパラジウム(0)存在下、トルエン中、加熱下反応させて、4 [4 (2 ジメチルアミノエトキシ)フェニル]ピペラジン 1 カルボン酸 t ブチルを得た。F: 350。

参考例２２

1 ベンジルピロリジン 3 オン及び N (2 アミノエチル)モルホリンを酢酸中、水素化トリアセトキシホウ素ナトリウムと室温にて反応させ、(1 ベンジルピロリジン 3 イル)(2 モルホリン 4 イルエチル)アミンを得た。F: 290。

【００５２】

参考例２３

2 シアノフェノール及び4 (2 クロロエチル)モルホリン塩酸塩のDMF溶液に炭酸カリウムを加え加熱下反応させ、4 [2 (2 シアノフェノキシ)エチル]モルホリンを得た。得られた化合物をTHF中、水素化リチウムアルミニウムと加熱下反応させ、4 [2 (2 アミノメチルフェノキシ)エチル]モルホリンを得た。F: 237。

参考例２４

2.6 ジクロロピラジンをN,N ジメチルイミダゾリジノン中、炭酸カリウムの存在下ピペラジン 1 カルボン酸 t ブチルエステルと加熱下反応させ、2 クロロ 6 (4 t ブトキシカルボニルピペラジン 1 イル)ピラジンを得た。F: 299。

参考例２５

6 (3 ベンジルオキシ 4 メトキシフェニル)ピリジン 2 カルボン酸メチルをTHF メタノール混合溶媒中、パラジウム炭素存在下、水素雰囲気下 して、6 (3 ヒドロキシ 4 メトキシフェニル)ピリジン 2 カルボン酸メチルを得た。得られた化合物を、DMF中、シクロプロピルメチルアロミド及び炭酸カリウムと加熱下反応させ、6 (3 シクロプロピルメトキシ 4 メトキシフェニル)ピリジン 2 カルボン酸メチルを得、更に、THF メタノール混合溶媒中、1M水酸化ナトリウム水溶液を加え加熱下反応させて、6 (3 シクロプロピルメトキシ 4 メトキシフェニル)ピリジン 2 カルボン酸を得た。FN: 294。

【００５３】

参考例２６

参考例２５と同様にして、6 (3 ジフルオロメトキシ 4 メトキシフェニル)ピリジン 2 カルボン酸を製造した。NMR1: 7.93 8.00 (2H. m). 7.01 (1H. d. J=8.0 Hz). 1.35 1.42 (1H. m).

参考例２７

参考例２６と同様にして、(4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェノキシ)酢酸 エチルを製造した。F: 506。

参考例２８

参考例２５と同様にして、5 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェノキシ)ペンタン酸 メチルを製造した。F: 534。

参考例２９

参考例２５と同様にして、4 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェノキシ)ブタン酸 エチルを製造した。F: 534。

参考例３０

参考例２５と同様にして、6 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニ

ル]ピペラジン 1 イル)フェノキシ)ヘキサン酸 エチルを製造した。F:562.
参考例 3 1
参考例 2 5 と同様にして、7 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェノキシ)ヘプタン酸 エチルを製造した。F: 576.
参考例 3 2
参考例 2 5 と同様にして、4 (3 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェノキシ)ブタン酸 エチルを製造した。F: 534.
参考例 3 3
参考例 2 5 と同様にして、5 (3 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェノキシ)ペンタン酸 メチルを製造した。F: 534.
参考例 3 4
参考例 2 5 と同様にして、6 (3 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェノキシ)ヘキサン酸 エチルを製造した。F: 562.
参考例 3 5
参考例 2 5 と同様にして、4 (2 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェノキシ)ブタン酸 エチルを製造した。F: 534.
参考例 3 6
参考例 2 5 と同様にして、5 (2 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェノキシ)ペンタン酸 メチルを製造した。F: 534.
参考例 3 7
参考例 2 5 と同様にして、6 (2 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェノキシ)ヘキサン酸 エチルを製造した。F: 562.
参考例 3 8
参考例 2 5 と同様にして、1 (t ブトキシカルボニル) 4 [2 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェノキシ)エチル]ピペラジンを製造した。F: 632.
参考例 3 9
参考例 2 5 と同様にして、4 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)アニリノ)ブタン酸 エチルを製造した。F: 533.
【0054】
参考例 4 0
6 クロロニコチン酸に塩化チオニルを加え加熱還流した。室温まで冷却した後減圧下濃縮した。ベンゼン、塩化アルミニウムを加え、100℃で加熱 した。以下常法にて後処理精製して得られた2 クロロ 5 ベンゾイルピリジンのDMF溶液にナトリウムメトキシドを加え加熱 した。以下常法にて後処理精製して2 メトキシ 5 ベンゾイルピリジンを得た。NMR1: 8.62 8.63 (1H.m). 7.77 7.80 (2H.m). 4.03 (3H.d.J=1.2Hz).
参考例 4 1
後記製造例 5 と同様にして、1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 一塩酸塩を得た。F:328.
参考例 4 2
後記製造例 5 と同様にして、4 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェニルカルバモイル)ピペリジン 1 カルボン酸 ベンジルを得た。F:664.
参考例 4 3
後記製造例 5 と同様にして、(±) trans 3 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 2.5 ジメチルピペラジン 1 イル}フェニル)プロピオン酸 エチルを得た。F: 532.
参考例 4 4
後記製造例 5 と同様にして、(±) trans 5 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 2.5 ジメチルピペラジン 1 イル}フェニル)ペンタン酸 エチルを得た

. F: 560.
【００５５】
参考例４５
４ブロモ２クロロアニソールのトルエン溶液に、１(ｔブトキシカルボニル)ピペラジン、トリス(ジベンジリデンアセトン)ジパラジウム(0)、2.2' ビス(ジフェニルホスフィノ)1.1' ビナフチル及びナトリウムｔブトキシドを加え、油浴温度110℃で4時間　した。以下常法により後処理精製して1(ｔブトキシカルボニル)４(３クロロ４メトキシフェニル)ピペラジンを得た。NMR1: 6.99 (1H.d.J=2.8Hz). 3.85 (3H.s). 1.48 (9H.s).
参考例４６
参考例４５と同様にして、１(ｔブトキシカルボニル)４(３フルオロ４メトキシフェニル)ピペラジンを得た。NMR1: 6.72 (1H.dd.J=14.2.8Hz). 3.85 (3H.s). 1.48 (9H.s).
参考例４７
参考例４５と同様にして、１(ベンゾフラン５イル)４(ｔブトキシカルボニル)ピペラジンを得た。NMR1: 7.58 (1H.d.J=2.4Hz). 3.07 3.09 (4H.m). 1.49 (9H.s).
参考例４８
参考例４５と同様にして、１(ｔブトキシカルボニル)４(４ジエチルアミノフェニル)ピペラジンを得た。F: 334.
【００５６】
参考例４９
１(ｔブトキシカルボニル)４(３クロロ４メトキシフェニル)ピペラジンのクロロホルム溶液にトリフルオロ酢酸を加え30分間　した。以下常法により後処理精製して、１(３クロロ４メトキシフェニル)ピペラジンを得た。F: 227.
参考例５０
参考例４９と同様にして、１(３フルオロ４メトキシフェニル)ピペラジンを得た。F: 211.
参考例５１
参考例４９と同様にして、１(３クロロピリジン２イル)ピペラジンを得た。NMR2: 8.26 (1H.d.J=2.4Hz). 7.97 (1H.d.J=2.4Hz). 2.81 2.84 (4H.m).
参考例５２
参考例４９と同様にして、ジエチル(４ピペラジノフェニル)アミンを得た。F: 234.
参考例５３
参考例４９と同様にして、(±) trans 3 [4 (2.5 ジメチルピペラジン１イル)フェニル]アクリロン酸　エチルを得た。F: 291.
参考例５４
参考例４９と同様にして、(±) trans 5 [4 (2.5 ジメチルピペラジン１イル)フェニル]ペンタン酸　エチルを得た。F: 319.
参考例５５
参考例４５及び参考例４９と同様にして、１(５メトキシピリジン３イル)ピペラジンを得た。NMR1: 7.96 (1H. d. J=2.4 Hz). 7.82 (1H. d. J=2.4 Hz). 3.84 (3H. s).
参考例５６
参考例４５及び参考例４９と同様にして、１(６メトキシピリジン３イル)ピペラジンを得た。
参考例５７
参考例４５及び参考例４９と同様にして、６ピペラジン１イルキノリンを得た。EI: 213.
参考例５８
参考例４５及び参考例４９と同様にして、１(６ブロモピリジン２イル)ピペラジンを得た。F: 242.
参考例５９
参考例４５及び参考例４９と同様にして、１(５ブロモピリジン２イル)ピペラジンを

得た．F：242．
【００５７】
参考例６０
６クロロニコチノニトリル及び(±) trans 2.5 ジメチルピペラジンのNMP溶液を油浴温度120℃で1時間　して、(±) trans 6 (2.5 ジメチルピペラジン 1 イル)ニコチノニトリルを得た．F：217．
参考例６１
参考例６０と同様にして、1 (4 ピペラジン 1 イル 2 トリフルオロメチルフェニル)エタノンを得た．F：273．
参考例６２
参考例６０と同様にして、(±) trans 1 [4 (2.5 ジメチルピペラジン 1 イル)フェニル]エタノンを得た．F：283．
参考例６３
参考例６０と同様にして、1 (2 ヒドロキシ 4 ピペラジン 1 イルフェニル)エタノンを得た．F：221．
参考例６４
参考例６０と同様にして、1 (5 ニトロピリジン 2 イル)ピペラジンを得た．F：209．
参考例６５
参考例６０と同様にして、(±) trans 4 (2.5 ジメチルピペラジン 1 イル)ベンズアルデヒドを得た．F：219．
【００５８】
参考例６６
4 フルオロベンズアルデヒドと1 (t アトキシカルボニル)ピペラジンのNMP溶液に炭酸カリウムを加え加熱　した．以下常法により後処理精製して、4 [4 (t アトキシカルボニル)ピペラジン 1 イル]ベンズアルデヒドを得た．NMR1：9.80 (1H.s). 3.37 3.40 (4H.m). 1.49 (9H.s)．
参考例６７
参考例６６と同様にして、2 クロロ 3 (4 t アトキシカルボニルピペラジン 1 イル)ピラジンを得た．NMR1：7.91 (1H.d.J=2.4Hz). 3.58 3.61 (4H.m). 1.49 (9H.s)．
参考例６８
参考例６６と同様にして、1 (4 アセチル 2 クロロフェニル) 4 (t アトキシカルボニル)ピペラジンを得た．NMR1：7.07 (1H.d.J=8.8Hz). 3.08 3.12 (4H.m). 1.49 (9H.s)．
参考例６９
参考例６６と同様にして、6 [4 (t アトキシカルボニル)ピペラジン 1 イル]ピリジン 3 カルバルデヒドを得た．NMR1：9.80 (1H.s). 3.54 3.58 (4H.m). 1.49 (9H.s)．
参考例７０
参考例６６と同様にして、6 [4 メチルピペラジン 1 イル]ピリジン 3 カルバルデヒドを得た．NMR1：9.78 (1H.s). 6.66 (1H.d.J=8.0Hz). 2.35 (3H.s)．
参考例７１
150℃で溶融させたピペラジンに2 クロロベンゾチアゾールを加え1時間　した．以下常法により後処理精製して、(ベンゾチアゾール 2 イル)ピペラジンを得た．F：220．
【００５９】
参考例７２
60%水素化ナトリウムとTHF混合物に、0℃冷却下、ジエチルホスホノ酢酸エチルを滴下し、更に4 [4 (t アトキシカルボニル)ピペラジン 1 イル]ベンズアルデヒドを滴下した．以下常法により後処理精製して、3 (4 [4 (t アトキシカルボニル)ピペラジン 1 イル]フェニル)アクリル酸エチルを得た．更に後記参考例９４と同様にして、3 (4 [4 (t アトキシカルボニル)ピペラジン 1 イル]フェニル)プロパン酸エチルを得た．NMR1：4.12 (2H.q.J=7.2Hz). 2.87 (2H.t.J=7.6Hz). 1.48 (9H.s)．
参考例７３

参考例７２と同様にして、３(６[４(ｔブトキシカルボニル)ピペラジン１イル]ピリジン３イル)アロパン酸エチルを得た。NMR1：6.80(1H.d.J=8.8Hz)．4.12(2H.q.J=7.2Hz)．2.56(2H.t.J=7.6Hz)。

参考例７４

参考例７２と同様にして、(±)trans３(４[１(ｔブトキシカルボニル)２.５ジメチルピペラジン４イル]フェニル)アロパン酸エチルを得た。EI：390。

【００６０】

参考例７５

参考例４９及び後記製造例５と同様の方法により、３(４[４[６(３.４ジメトキシフェニル)ピリジン２カルボニル]ピペラジン１イル)フェニル)アロパン酸エチルを得た。NMR1：6.97(1H.d.J=8.4Hz)．4.12(2H.q.J=7.2Hz)．2.89(2H.t.J=7.6Hz)。

参考例７６

参考例７５と同様にして、５(４[４[６(３.４ジメトキシフェニル)ピリジン２カルボニル]ピペラジン１イル)フェニル)ペンタン酸エチルを得た。NMR1：6.97(1H.d.J=8.8Hz)．4.12(2H.q.J=7.2Hz)．2.31(2H.t.J=7.2Hz)。

参考例７７

参考例７５と同様にして、３(６[４[６(３.４ジメトキシフェニル)ピリジン２カルボニル]ピペラジン１イル)ピリジン３イル)アロパン酸エチルを得た。NMR1：6.97(1H.d.J=8.8Hz)．4.12(2H.q.J=7.2Hz)．2.84(2H.t.J=7.6Hz)。

参考例７８

６クロロニコチン酸メチルとピペラジンのDMSO溶液を油浴温度120℃で　して、６ピペラジン１イルニコチン酸メチルを得た。F：222。

参考例７９

２ニトロ５フルオロフェノールより参考例２５及び参考例６６と同様の反応により、１(３ベンジルオキシ４ニトロフェニル)４(ｔブトキシカルボニル)ピペラジンを得た。NMR1：8.01(1H.d.J=8.4Hz)．5.22(2H.s)．1.49(9H.s)。

【００６１】

参考例８０

１(３ベンジルオキシ４ニトロフェニル)４(ｔブトキシカルボニル)ピペラジンのメタノールTHF混合溶液にパラジウム炭素を加え水素雰囲気下　した。以下常法により後処理精製して得られた２アミノ５[１(ｔブトキシカルボニル)ピペラジン４イル]フェノールのメタノール溶液にオルトギ酸メチル、ｐトルエンスルホン酸を加え加熱　した。以下常法により後処理精製して、６(４ｔブトキシカルボニルピペラジン１イル)ベンゾオキサゾールを得た。NMR1：7.97(1H.s)．3.15 3.19(4H.m)．1.49(9H.s)。

参考例８１

４.６ジクロロピリミジンより参考例８０及び参考例４９と同様の方法により、４クロロ６ピペラジン１イルピリミジンを得た。F：199。

参考例８２

Ｎ－ベンジルイミノ二酢酸をTHF中、CDI及び５アミノインドールと反応させ、４ベンジル１(１Hインドール５イル)ピペラジン２.６ジオンを得、次いでTHF中、水素化リチウムアルミニウムと反応させた。得られた化合物のエタノール溶液に濃塩酸、水酸化パラジウムを加え、３気圧の水素雰囲気下65時間反応させて、５ピペラジン１イル１Hインドールを得た。EI：201。

参考例８３

４(２クロロピリミジン４イル)ピペラジン１カルボアルデヒド及び２(ジメチルアミノ)エタノールをカリウムｔブトキシド存在下、DMF中反応して得られた化合物を、メタノール中に炭酸カリウム存在下、80℃で24時間反応させ、Ｎ,Ｎジメチル Ｎ(２[(４ピペラジン１イルピリミジン２イル)オキシ]エチル)アミンを得た。F：252。

【００６２】

参考例８４

4 [4 (t アトキシカルボニル)ピペラジン 1 イル]ベンズアルデヒド及び[3 (エトキシカルボニル)プロピル]トリフェニルホスホニウムブロミドを、THF中t アトキシカリウム存在下反応させ、5 (4 [4 (t アトキシカルボニル)ピペラジン 1 イル]フェニル) 4 ペンテン酸エチルを得、次いで、後記参考例９４と同様にして、5 (4 [4 (t アトキシカルボニル)ピペラジン 1 イル]フェニル)ペンタン酸エチルを得た。NMR1: 4.12 (2H.q.J=7.2Hz). 2.31 (2H.t.J=7.2Hz). 1.48 (9H.s).

参考例８５

参考例８４と同様にして、5 (6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ピリジン 3 イル)ペンタン酸エチルを得た。NMR1: 8.02 (1H.d.J=2.4Hz). 4.12 (2H.q.J=7.2Hz). 1.48 (9H.s).

参考例８６

参考例８４と同様にして、(±) trans 1 (t アトキシカルボニル) 4 [4 (4 エトキシカルボニルアミノ)フェニル] 2.5 ジメチルピペラジンを得た。FN: 417.

参考例８７

2 ブロモ 6 ヨードピリジン 3 オールを炭酸カリウム及び臭化ベンジルと反応させ、3 (ベンジルオキシ) 2 ブロモ 6 ヨードピリジンを得、次いで、参考例４５、製造例４３、製造例５及び参考例９４と同様に順次処理して、6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ピリジン 3 オールを得た。F: 421.

【００６３】

参考例８８

2 ブロモ 6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ピリジン 3 オールのDMF溶液に60%水素化ナトリウム及び4 ブロモブタン酸エチルを加え室温で1時間反応させた。以下常法により後処理精製して、4 [(2 ブロモ 6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル) 3 ピリジル)オキシ]ブタン酸エチルを得た。F: 535.

参考例８９

4 (2 クロロピリミジン 4 イル)ピペラジン 1 カルボアルデヒド及びベンジルアルコールより、参考例８３、製造例５、参考例９４及び参考例８８と同様の方法により順次処理して、4 (4 [4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル} 2 オキソ 1.2 ジヒドロピリミジン 1 イル)ブタン酸エチルを得た。F: 536.

参考例９０

4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 1 (4 ヒドロキシフェニル)ピペラジンに1.2 ジブロモエタン、2M 水酸化ナトリウム水溶液、テトラ n ブチルアンモニウム硫酸水素塩及び水を加え、60℃で　した。反応液を冷却後、水及びクロロホルムを加え、不溶物を　去した。以下常法により後処理精製して、1 [4 (2 ブロモエトキシ)フェニル] 4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジンを得た。F: 526.

【００６４】

参考例９１

2.5 ジブロモピリジン及び2 (ジメチルアミノ)エタノールのDMF溶液にカリウムt アトキシドを加え、油浴温度100℃で3時間　して、N (2 [(5 ブロモピリジン 2 イル)オキシ]エチル) N.N ジメチルアミンを得、更に参考例５５と同様にして、N.N ジメチル N (2 [(5 ピペラジン 1 イルピリジン 2 イル)オキシ]エチル)アミンを得た。F: 251.

参考例９２

2 (ベンジルオキシ) 6 ブロモナフタレンを用い、参考例４５、製造例４３及び製造例５と同様に順次処理して、1 [6 (ベンジルオキシ) 2 ナフチル] 4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジンを得た。この化合物をトリフルオロ酢酸に溶解し、氷冷下ペンタメチルベンゼンを加え、室温で2時間、更に油浴温度40℃で2時間して、6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル) 2 ナフトールを得た。F: 470.

参考例９３
６ピリジン３カルボキサルデヒドのジオキサン溶液に酢酸パラジウムトリフェニルホスフィン、アクリル酸メチル及び炭酸セシウムを加え加熱還流した。以下常法により後処理精製して、３(５ホルミルピリジン２イル)アクリル酸メチルを得た。NMR1：10.13(1H.s)．7.08(1H.d.J=15.6Hz)．3.85(3H.s)．
【００６５】
参考例９４
３(５ホルミルピリジン２イル)アクリル酸メチルの酢酸エチル エタノール溶液にパラジウム炭素を加え水素雰囲気下 した。以下常法により後処理精製して、３(５ホルミルピリジン２イル)プロパン酸メチルを得た。NMR1：10.29(1H.s)．3.68(3H.s)．2.88(2H.t.J=7.2Hz)．
参考例９５
(±)trans４(2.5ジメチルピペラジン１イル)ベンズアルデヒドのアセトニトリル溶液にジ(t アトキシカルボニル)ジカルボネート及び4ジメチルアミノピリジンを加えた。以下常法により後処理精製して、(±)trans１(t アトキシカルボニル)４(４ホルミルフェニル)2.5ジメチルピペラジン１カルボン酸 t ブチルを得た。F：319．
参考例９６
フルオロ４ニトロベンゼン及び(±)trans 2.5ジメチルピペラジンのNMP溶液を油浴温度120℃で30分間 して、(±)trans 2.5ジメチル１(４ニトロフェニル)ピペラジンを得、更に製造例５と同様にして、(±)trans１[6(3.4ジメトキシフェニル)ピリジン２カルボニル]2.5ジメチル４(４ニトロフェニル)ピペラジンを得た。F：477．
参考例９７
６クロロキノリン１オキシドの無水酢酸溶液に、３オキソ酪酸メチルを加え、油浴温度40℃で30分間 し、得られた化合物を10%塩酸に加え室温で反応させ、(6クロロキノリン２イル)酢酸メチルを得た。この化合物を更に、参考例４５、製造例４３及び製造例５と同様に順次処理して、6(4[6(3.4ジメトキシフェニル)ピリジン２カルボニル]ピペラジン１イル)キノリン２イル]酢酸メチルを得た。F：527．
参考例９８
後記製造例１０と同様にして、4[N(4(4[6(3.4ジメトキシフェニル)ピリジン２カルボニル]ピペラジン１イル)フェニル)Nメチルアミノ]ブタン酸 エチルを得た。F：547．
【００６６】
製造例１
２オキソ３フェニルピペラジン 740 mgのTHF 20 ml溶液に水素化リチウムアルミニウム 638 mgを加え、3時間加熱還流した。反応液を氷冷し、硫酸ナトリウム10水和物を反応液中にゲルがなくなるまで加え、しばらく した後不溶物を 去した。溶媒を留去して得た粗製の２フェニルピペラジンを、6(3.4ジメトキシフェニル)ピリジン２カルボン酸 500 mgのTHF 20 ml溶液に加え、更にWSC塩酸塩 556 mg及びHOBt 260 mgを加え、室温で2日間 した。反応液に酢酸エチルを加え、水、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。得られた残 をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、無色無定型結晶(670 mg)を得た。この化合物をエタノールに溶解し、フマル酸 192 mgを加えてフマル酸塩とした後、エタノール 酢酸エチルから再結晶を行って、２(3.4ジメトキシフェニル)6(3フェニルピペラジン１カルボニル)ピリジン 0.5フマル酸塩 607 mgを無色結晶として得た。
製造例２
6(3.4ジメトキシフェニル)ピリジン２カルボン酸 500 mgのTHF 20 ml溶液に氷冷下、塩化オキサリル0.18 ml及びDMF 1滴を加えた。30分 後、反応液を、4(4メトキシフェニル)ピペラジン 370 mgのピリジン 10 ml溶液に氷冷下滴下した。室温まで昇温して更に30分 した。反応液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後溶媒を留去した。残 をシリカゲルカラムクロマト

グラフィー(クロロホルム メタノール)で精製し、更に酢酸エチル アセトニトリルから再結晶を行い、1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 4 (4 メトキシフェニル)ピペラジン 370 mgを無色結晶として得た。

【0067】

製造例3

4 [4 (2 ジメチルアミノエトキシ)フェニル]ピペラジン 1 カルボン酸t ブチル 0.62 gを4N塩化水素/酢酸エチル溶液 15 ml中反応させた。溶媒を留去して得られた粗生成物 0.88 gのDMF 15 ml溶液に、WSC塩酸塩 0.34 g、HOBt 0.24 g及び6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸 0.41 gを加え、室温下65時間反応させた。更にWSC塩酸塩 0.34 g、HOBt 0.24 g及びトリエチルアミン 0.50 mlを加え、室温下8.5時間 した。反応液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(酢酸エチル)で精製後、得られた化合物をシュウ酸 106 mgにより造塩し、再結晶(エタノール)して、1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 4 [4 (2 ジメチルアミノエトキシ)フェニル]ピペラジン ニシュウ酸塩 253 mgを淡黄色結晶として得た。

製造例4

1 ベンジル 4 ベンゾイルピペリジン 4.50 gのピリジン 50 ml溶液に、ヒドロキシルアミン塩酸塩 3.00 gを加え、油浴温度80℃で1時間 した。室温まで冷却後、1M水酸化ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 をジイソプロピルエーテルで洗浄して得た1 ベンジル ピペリジン 4 イル フェニル ケトン オキシム 3.50 gを、THF 50 mlに溶解し、油浴温度80℃で、水素化アルミニウムリチウム 6.50 gを徐々に加えた。そのまま30分 後、油浴温度80℃で30分加熱した。氷冷下、メタノール 10 ml及び無水硫酸ナトリウムを順次加えた。不溶物を 過し、 液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製して得た4 (α アミノベンジル) 1 ベンジルピペリジン 1.03 gと、6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸 1.00 gを用い、製造例2と同様の方法により、N [(1 ベンジルピペリジン 4 イル)(フェニル)メチル] 6 (3.4 ジメトキシフェニル)ピリジン 2 カルボキサミド 620 mgを無色結晶として得た。

【0068】

製造例5

6 (3.4 ジメトキシフェニル) ピリジン 2 カルボン酸 1.20 g、フェニル(ピリジン 4 イル)メチルアミン 850 mgのDMF 20 ml溶液に、WSC塩酸塩 960 mg、HOBt 800mg及びトリエチルアミン 0.72 mlを室温で加えた。2時間 後、水を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去後、残 をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、更に酢酸エチルから再結晶を行い、6 (3.4 ジメトキシフェニル) N [フェニル(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド 1.25 gを無色結晶として得た。

製造例6

6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸 500 mgのTHF 5 ml溶液に塩化オキサリル 0.34 ml及び触媒量のDMFを加え、室温で1時間 した。反応液の溶媒を留去し、残 をアセトニトリル 10 ml溶液とし、2.2 ジフェニルグリシン 440 mg、トリエチルアミン 0.80 ml及び4 (ジメチルアミノ)ピリジン 24 mgを加え、室温で16時間 した。不溶物を 取し、エタノールで洗浄して、無色結晶(199 mg)を得た。この化合物に1N塩酸水溶液を加え、クロロホルムで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥し、溶媒を留去した。得られた粗結晶をアセトニトリル及びジイソプロピルエーテルで順次洗浄し、([6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]アミノ)(ジフェニル)酢酸 119 mgを無色結晶として得た。

【0069】

製造例７

６(3.4 ジメトキシフェニル) Ｎ[(2 ベンジルオキシフェニル)(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド 5.25 9をトリフルオロ酢酸 40 ml に溶解させ、ベンタメチルベンゼン 4.39 9と室温～50℃で5日間　した。反応液を留去後、炭酸水素ナトリウム水溶液を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム エタノール)で精製して、更に再結晶(2 プロパノール)して、６(3.4 ジメトキシフェニル) Ｎ[(2 ヒドロキシフェニル)(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド 1.028 9を無色結晶として得た。

製造例８

６(3.4 ジメトキシフェニル) Ｎ[(2 ヒドロキシフェニル)(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド 0.25 9をDMF 5 mlに溶解させ、炭酸カリウム 0.15 9存在下、ヨウ化メチル 40 mlと室温で5時間反応させた。反応液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(酢酸エチル)で精製し、得られた化合物を4M塩化水素／酢酸エチル溶液で処理し塩場した後、再結晶(エタノール)して、６(3.4 ジメトキシフェニル) Ｎ[(2 メトキシフェニル)(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド 一塩酸塩 157 mgを無色結晶として得た。

【００７０】

製造例９

Ｎ(1 ベンジル 4 フェニルピペリジン 4 イル) ６(3.4 ジメトキシフェニル)ピリジン 2 カルボキサミド 250 mgのジクロロエタン 3 ml溶液に、クロロぎ酸1 クロロエチル0.18 mlを室温で加えた。30分　した後、溶媒を留去し、メタノール10mlを加え30分　した。3M塩酸を加えエーテルで洗浄後、1 M水酸化ナトリウムで塩基性とした。クロロホルムで抽出し、有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製して得た生成物(150 mg)をメタノールに溶解し、フマル酸 40 mgを加え溶媒を留去した。得られた粗結晶をアセトニトリル エタノールから再結晶して、６(3.4 ジメトキシフェニル) Ｎ(4 フェニルピペリジン 4 イル)ピリジン 2 カルボキサミドのーフマル酸塩 1.5水和物 53 mgを無色結晶性固体として得た。

製造例１０

６(3.4 ジメトキシフェニル) Ｎ(4 フェニルピペリジン 4 イル)ピリジン 2 カルボキサミド 500 mgのメタノール 10 ml溶液に、35%ホルマリン水溶液 0.5 ml、酢酸 0.5 ml及びトリアセトキシ水素化ホウ素ナトリウム 300 mgを加えた。30分　後、更にトリアセトキシ水素化ホウ素ナトリウム 100 mgを加え、30分　した。1 M水酸化ナトリウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール アンモニア水)で精製して得た生成物(440 mg)をメタノールに溶解し、フマル酸 120 mgを加え、溶媒を留去した。アセトニトリル エタノールから再結晶して、６(3.4 ジメトキシフェニル) Ｎ(1 メチル 4 フェニルピペリジン 4 イル)ピリジン 2 カルボキサミド ーフマル酸塩 890 mgを無色結晶として得た。

【００７１】

製造例１１

Ｎ[2 (トリメチルシリル)エトキシカルボニル] 1 ベンジル 4 メチル 4 ピペリジルアミン 1.35 9の1.4 ジオキサン 15 ml溶液に、1Mフッ化テトラブチルアンモニウム／THF溶液 5.0 mlを加え、油浴温度70℃で13時間　した。更に1Mフッ化テトラブチルアンモニウム／THF溶液 2.0 mlを加え、油浴温度70℃で1日間　した。反応液の溶媒を留去して得られた残　に酢酸エチルを加え、1M 塩酸水溶液で抽出した。水層を炭酸水素ナトリウムで中和した後、クロロホルムで抽出した。有機層を無水硫酸ナトリウムで乾燥し、溶媒を留去して、粗製の1 ベンジル 4 メチルピペリジン 4 イルアミンを得た。この化合物を

用い、以下、製造例１に記載のアミド化反応と同様にして、Ｎ（１ベンジル ４ メチル ４ ピペリジル）６（３,４ ジメトキシフェニル）ピリジン ２ カルボキサミド 一シュウ酸塩 450 ｍｇを無色結晶として得た。

製造例１２

１ベンジル Ｎ（ベンジルオキシカルボニル）４（モルホリン ４イルカルボニルメチル）ピペリジン ４イルアミン 800 ｍｇのエタノール 20 ｍｌ溶液に、10％パラジウム炭素 80 ｍｇ及び蟻酸アンモニウム 300 ｍｇを加え、油浴温度70℃で17時間　　した。反応液から不溶物を　去し、溶媒を留去して、粗製の１ベンジル ４（モルホリン ４イルカルボニルメチル）ピペリジン ４イルアミン 549 ｍｇを淡黄色油状物として得た。水素化リチウムアルミニウム 400 ｍｇとＴＨＦ 10 ｍｌ混合物の加熱還流下に、得られた化合物のＴＨＦ 5 ｍｌ溶液を滴下し、そのまま30分間加熱還流した。反応液を氷冷し、硫酸ナトリウム10水和物を反応液中にゲルがなくなるまで加え、しばらく　　後不溶物を　去した。溶媒を留去して粗製の１ベンジル ４［２（モルホリン ４イル）エチル］ピペリジン ４イルアミン 427 ｍｇを淡黄色油状物として得た。

６（３,４ ジメトキシフェニル）ピリジン ２ カルボン酸 360 ｍｇのＴＨＦ 5 ｍｌ溶液に、塩化オキサリル 0.25 ｍｌ及び触媒量のＤＭＦを加え、室温で15分間　　した。溶媒を留去して得られた残　をＴＨＦ 10 ｍｌに溶解し、先に得られた１ベンジル ４［２（モルホリン ４イル）エチル］ピペリジン ４イルアミン及びトリエチルアミン 0.50 ｍｌを加え、室温で14時間した。反応液に飽和重曹水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥し、溶媒を留去した。得られた残　をシリカゲルカラムクロマトグラフィー（クロロホルム メタノール）で精製し、黄色無定型結晶（415 ｍｇ）を得た。この化合物をメタノールに溶解し、フマル酸 176 ｍｇを加えてフマル酸塩とした後、イソプロパノールから再結晶して、Ｎ［１ベンジル ４［２（モルホリン ４イル）エチル］ピペリジン ４イル］６（３,４ ジメトキシフェニル）ピリジン ２ カルボキサミド ニフマル酸塩 一水和物 364 ｍｇを無色結晶として得た。

【００７２】

製造例１３

１ベンジル ４［［６（３,４ ジメトキシフェニル）ピリジン ２ カルボニル］アミノ］ピペリジン ４ カルボン酸メチル 1.70 ｇのＴＨＦ 30 ｍｌ溶液に水素化ホウ素ナトリウム 500 ｍｇを加えた。油浴温度70℃でメタノール 5 ｍｌを滴下し30分　　した。室温まで冷却後、水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、硫酸マグネシウムにより乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー（クロロホルム メタノール）で精製し、更に再結晶（イソプロピルエーテル 酢酸エチル）して、Ｎ（１ベンジル ４ ヒドロキシメチルピペリジン ４イル）６（３,４ ジメトキシフェニル）ピリジン ２ カルボキサミド 720 ｍｇを無色結晶として得た。

製造例１４

６（３,４ ジメトキシフェニル）Ｎ（４フェニルピペリジン ４イル）ピリジン ２ カルボキサミド 0.18 ｇをＤＭＦ 3.5 ｍｌ中、炭酸セシウム 140 ｍｇの存在下、酢酸（２クロロメチル）フェニル 70 ｍｇと室温にて20時間反応させた。常法により後処理をして得た粗生成物をＴＨＦ 10 ｍｌ中、1Ｍ水酸化ナトリウム水溶液 3 ｍｌと室温～50℃で16.5時間反応させた。反応液を1Ｍ塩酸水溶液で中和にした後、炭酸水素ナトリウム水溶液でｐＨを約8とし、酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー（ヘキサン 酢酸エチル）で精製し、更に再結晶（エタノール ジエチルエーテル）して、６（３,４ ジメトキシフェニル）Ｎ［１（２ヒドロキシベンジル）４フェニル ４ピペリジル］ピリジン ２ カルボキサミド 一水和物 85 ｍｇを無色結晶として得た。

【００７３】

製造例１５

６（３,４ ジメトキシフェニル）ピリジン ２ カルボン酸 500 ｍｇのＴＨＦ 10 ｍｌ溶液に、ＣＤＩ 373 ｍｇを加え、油浴温度60℃で1時間　　した。反応液に０ベンジルヒドロキシルアミン塩

酸塩 367 mg及びトリエチルアミン 0.32 mlを加え、油浴温度60℃で3時間　した。反応液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥し、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(ヘキサン酢酸エチル)で精製し、更に酢酸エチル ジイソプロピルエーテルから再結晶して、N ベンジルオキシ 6 (3.4 ジメトキシフェニル)ピリジン 2 カルボキサミド 566 mgを無色結晶として得た。

製造例16

N ベンジルオキシ 6 (3.4 ジメトキシフェニル)ピリジン 2 カルボキサミド 400 mgのベンゼン 10 ml溶液に、10%パラジウム炭素 50 mg及びシクロヘキセン 5 mlを加え、油浴温度80℃で4時間　した。不溶物を　去し、溶媒を留去して得られた残　をエタノール 10 mlに溶解し、10%パラジウム炭素 40 mg及びギ酸アンモニウム 150 mgを加え、油浴温度70℃で2時間　した。不溶物を　去し、溶媒を留去して得られた残　に酢酸エチルを加え、1N水酸化ナトリウム水溶液で抽出した。水層を1N塩酸水溶液でpH 4に調整し、クロロホルムで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥し、溶媒を留去した。得られた残　をアセトニトリルから再結晶して、6 (3.4 ジメトキシフェニル) N ヒドロキシピリジン 2 カルボキサミド 108 mgを微茶褐色結晶として得た。

【0074】

製造例17

6 (3.4 ジメトキシフェニル) N [フェニル(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド1.00 gのジクロロメタン10 ml溶液に、氷冷下m クロロ過安息香酸400 mgを加え氷冷下30分　した。更に、m クロロ過安息香酸400 mgを加え、30分　した。更に、m クロロ過安息香酸400 mgを加えた後、室温まで昇温し30分　した。反応液に水を加え、クロロホルムで抽出し、有機層を水、飽和チオ硫酸ナトリウム水溶液、飽和食塩水で洗浄した。有機層を無水硫酸マグネシウムで乾燥後溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、次いで、アセトニトリル 酢酸エチルから再結晶して、6 (3.4 ジメトキシフェニル) N [フェニル(ピリジン 4 イル)メチル]ピリジン 2 カルボキサミド1.25 gを無色結晶として得た。

製造例18

(N [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] N (1.2.3.4 テトラヒドロナフタレン 1 イル)アミノ)酢酸メチル 620 mgのメタノール 10 ml溶液に、1N 水酸化ナトリウム水溶液 3 ml及びTHF 10 mlを加え、室温で18時間　した。反応液に1N 塩酸水溶液 3 mlを加え、溶媒を留去した。残　を水で洗浄し、得られた粗結晶をエタノールから再結晶を行い、(N [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] N (1.2.3.4 テトラヒドロナフタレン 1 イル)アミノ)酢酸 472 mgを無色結晶として得た。

【0075】

製造例19

シクロペンタノン 0.50 mlの酢酸 5 ml溶液に2 メトキシエチルアミン 0.32 ml及び水素化トリアセトキシホウ素ナトリウム 1.20 gを加え、室温で30分間　した。反応液にトルエンを加え、溶媒を留去し、得られた残　に1N水酸化ナトリウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去して得られた粗製のN (2 メトキシエチル)シクロペンチルアミンと、6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸 400 mgを用い、製造例5と同様の方法により、N シクロペンチル 6 (3.4 ジメトキシフェニル) N (2 メトキシエチル)ピリジン 2 カルボキサミド 215 mgを無色油状物として得た。

製造例20

2 クロロ 6 (4 t アトキシカルボニルピペラジン 1 イル)ピラジン0.71 gを4M塩酸 酢酸エチル溶液15 ml中、室温下7時間　した。溶媒を留去し、2 クロロ 6 (ピペラジン 1 イル)ピラジン塩酸塩の粗生成物を得た。得られた粗生成物と6 (3.4 ジメトキシフェニル)ピリジン 2 カルボン酸0.62 gを製造例5と同様の方法により、2 クロロ 6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ピラジン594 mgを淡

黄色結晶として得た。

【００７６】

製造例２１

１[６(３.４ ジメトキシフェニル)ピリジン ２ カルボニル]４(ピリジン ４ イル)ピペラジン353 m9のジクロロメタン10 ml溶液に、m クロロ過安息香酸195 m9を加え5℃で１時間 した。反応液にチオ硫酸ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を水及び飽和食塩水で洗浄、次いで硫酸マグネシウムにより乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー（クロロホルム メタノール）で精製し、次いで再結晶（エタノール 酢酸エチル）して、１[６(３.４ ジメトキシフェニル)ピリジン ２ カルボニル]４(１ オキシドピリジン ４ イル)ピペラジン 1.5水和物 294 m9を淡黄色結晶として得た。

製造例２２

１[６(３.４ ジメトキシフェニル)ピリジン ２ カルボニル]４(４ ニトロフェニル)ピペラジン ２.５９のエタノール70 ml及び水25 ml混合溶液に塩化アンモニウム ０.１５９と還元鉄 ３.１９を加え、２時間加熱還流した。反応液をセライトを用いて 過し、 液を減圧濃縮し、得られた残 に飽和炭酸水素ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、更にアセトニトリル 酢酸エチルより結晶化させ、１[６(３.４ ジメトキシフェニル)ピリジン ２ カルボニル]４(４ アミノフェニル)ピペラジン ２.１９を淡桃色結晶として得た。

【００７７】

製造例２３

６ブロモ ２.３ ジヒドロ １.４ ベンゾジオキシン500 m9のTHF １０ ml溶液に ７８℃で１.６ M n ブチルリチウム／n ヘキサン溶液1.７５ mlを加えた。７８℃で１時間 した後、ホウ酸トリメチル0.７８ mlを加え徐々に室温に昇温しながら15時間 した。反応液の溶媒を留去し、残 をジメトキシエタン１０ mlに溶解し、エタノール ２ ml、N（インダン １ イル）６ブロモピリジン ２ カルボキサミド ５００ m9、酢酸パラジウム(II) ３０ m9、トリフェニルホスフィン １５０ m9及び炭酸ナトリウム ３３５ m9の水 ２ ml溶液を加え、５時間加熱還流した。不溶物を 去後、溶媒を留去して得られた残 に酢酸エチルを加え、飽和重曹水、飽和食塩水で洗浄後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(ヘキサン 酢酸エチル)で精製し、更に酢酸エチル ジイソプロピルエーテルから再結晶して、６(２.３ ジヒドロ １.４ ベンゾジオキシン ６ イル）N（インダン １ イル)ピリジン ２ カルボキサミド320 m9を無色結晶として得た。

製造例２４

６(４ヒドロキシ ３ メトキシフェニル）N インダン １ イルピリジン ２ カルボキサミド 320 m9のDMF ５ ml溶液に、氷冷下、(２ クロロエチル)ジメチルアミン塩酸塩 ２００ m9及び60%水素化ナトリウム ９１ m9を加え、油浴温度80℃で1.５日間 した。溶媒を留去し、得られた残 に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(クロロホルム～クロロホルム メタノール)で精製し、茶褐色油状物 １０６ m9を得た。この化合物をエタノール ２ mlに溶解し、フマル酸 ２８ m9を加えてフマル酸塩とした後、エタノール 酢酸エチルから再結晶して、６[４(２ ジメチルアミノエトキシ）３ メトキシフェニル]N インダン １ イルピリジン ２ カルボキサミド 一フマル酸塩 １０４ m9を無色結晶として得た。

【００７８】

製造例２５

６(４ヒドロキシ ３ メトキシフェニル）N インダン １ イルピリジン ２ カルボキサミド 310 m9の２ プタノン １０ ml溶液に、３ クロロメチルピリジン塩酸塩 １７０ m9及び炭酸カリウム ２７８ m9を加え、油浴温度60℃で13時間 し、更に油浴温度80℃で１日間 した。反応液の溶媒を留去し、得られた残 に水を加え、酢酸エチルで抽出した。有機層を飽和

食塩水で洗浄し、無水硫酸マグネシウムで乾燥し、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(ヘキサン 酢酸エチル～クロロホルム メタノール)で精製し、更に酢酸エチル ジイソプロピルエーテルから再結晶して、Nインデン 1イル 6[3メトキシ 4(ピリジン 3イルメトキシ)フェニル]ピリジン 2カルボキサミド 110 m9を無色結晶として得た。

製造例26

6(3ヒドロキシ 4メトキシフェニル)N(インデン 1イル)ピリジン 2カルボキサミド 360 m9のTHF 10 ml及びDMF 10 ml溶液にアロモ酢酸エチル 120 m9及び炭酸カリウム 690 m9を加え、50℃で5時間 した。溶媒を留去後、水を加え酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後溶媒を留去した。得られた粗生成物のエタノール10 ml溶液に1M水酸化ナトリウム水溶液 7 mlを加え室温で2時間反応させた。反応液に1M塩酸水溶液を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 を酢酸エチル ジエチルエーテルから再結晶して、{5[6(インデン 1イルカルバモイル)ピリジン 2イル]2メトキシフェノキシ}酢酸 245 m9を無色結晶として得た。

【0079】

製造例27

6(3ヒドロキシ 4メトキシフェニル)N(インデン 1イル)ピリジン 2カルボキサミド 360 m9のTHF 10ml及びDMF 10 ml溶液に塩化2ジメチルアミノエチル塩酸塩 144 m9及び炭酸カリウム 690 m9を加え、50℃で5時間 した。溶媒を留去後、水を加え酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 をジエチルエーテルで結晶化させた後、エタノール ジエチルエーテルから再結晶して、6[3(2ジメトキシアミノエトキシ)4メトキシフェニル]N(インデン 1イル)ピリジン 2カルボキサミド 110 m9を無色結晶として得た。

製造例28

6(3アミノ 4メトキシフェニル)Nインデン 1イルピリジン 2カルボキサミド 1.00 9のピリジン 15 ml溶液に、氷冷下、塩化アセチル 0.22 mlの塩化メチレン 5 ml溶液を加えた。室温で1.5時間 後、溶媒を留去し、残 に水を加え酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 をエタノールから再結晶して、6(3アセチルアミノ 4メトキシフェニル)Nインデン 1イルピリジン 2カルボキサミド 829 m9を無色結晶として得た。

【0080】

製造例29

6(3エチル 4ビニルフェニル)Nインデン 1イルピリジン 2カルボキサミド 205 m9のエタノール 5 ml溶液に、10%パラジウム炭素 30 m9を加え、常圧の水素雰囲気下、室温で17時間 した。不溶物を 去し、溶媒を留去し得られた残 をシリカゲルカラムクロマトグラフィー(ヘキサン 酢酸エチル)で精製して、6(3,4ジエチルフェニル)Nインデン 1イルピリジン 2カルボキサミド 186 m9を無色油状物として得た。

製造例30

6(3アミノ 4メトキシフェニル)Nインデン 1イルピリジン 2カルボキサミド 0.759のエタノール 10 ml溶液に、1Hベンゾトリアゾール 1メタノール 812 m9を加え、室温下19時間 した。析出した黄色固体を 取し、THF 5 mlに懸濁させ、水素化ホウ素ナトリウム 74 m9を加えた。室温下1.5時間激しく 後、飽和炭酸水素ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸マグネシウムにより乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(ヘキサン 酢酸エチル)で精製し、得られた化合物をエタノール中でシュウ酸塩として、Nインデン 1イル 6(4メトキシ 3メチルアミノフェニル)ピリジン 2カルボキサミド ーシュウ酸塩 一水和物 30 m9を無色結晶として得た。

【0081】

製造例31

6 (4 メトキシ 3 ニトロフェニル) N インダン 1 イル]ピリジン 2 カルボキサミド 0.3 7 9のTHF 5 ml及びメタノール 5 ml溶液に、10%パラジウム炭素 0.40 9を加え、水素雰囲気中で　した。65 mlの水素消費後、37%ホルムアルデヒド水溶液 1.96 ml及び酢酸 3 mlを加え、水素雰囲気下室温にて　した。反応液をセライト　過し、　液に炭酸水素ナトリウム水溶液を加え酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸マグネシウムにより乾燥後、溶媒を留去した。残　に4N塩化水素／酢酸エチル溶液を加え、溶媒を留去して得られた残　を熱ジイソプロピルエーテルで洗浄して、6 (4 メトキシ 3 ジメチルアミノフェニル) N インダン 1 イル]ピリジン 2 カルボキサミド 一塩酸塩 二水和物 101 m9を淡褐色結晶として得た。

製造例3 2

1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 一塩酸塩 327 m9のエタノール 6 ml溶液に、トリエチルアミン 0.28 ml及び2.4 ジクロロピリミジン 148 m9を加え、油浴温度90℃で2時間　した。溶媒を留去後、水を加えクロロホルムで抽出した。有機層を水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(ヘキサン 酢酸エチル)で精製し、更にアセトニトリル ジイソプロピルエーテルから再結晶して、2 クロロ 4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ピリミジン 一水和物 70 m9を無色結晶として得た。

【００８２】

製造例3 3

4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)安息香酸 171 m9のTHF 5 ml溶液にCDI 63 m9を加え、60℃で　した。さらにCDI 52 m9を2回に分けて加え、合計24時間60℃で　した。反応液を室温まで冷却後、アンモニア水 0.25 mlを加え、6時間室温で　し、更にアンモニア水 0.5 mlを加え、室温で　した。析出した結晶を　取し、メタノール THFから再結晶して、4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ベンザミド 68 m9を無色結晶として得た。

製造例3 4

4 (4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェニルカルバモイル)ピペリジン 1 カルボン酸 ベンジル 159 m9のエタノール 8 mlとTHF 8 mlの混合溶媒にアルゴン雰囲気下、10%パラジウム炭素 18 m9を加えた。常圧水素雰囲気下、2時間室温で　後、セライトを用いて　過し、　液を減圧濃縮した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール アンモニア水)で精製し、アセトニトリルから結晶化して、4' (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ピペリジン 4 カルボキシアニリド 70 m9を無色結晶として得た。

【００８３】

製造例3 5

1 (ベンゾフラン 5 イル) 4 (t アトキシカルボニル)ピペラジン1.20 9のクロロホルム 5 ml溶液に0℃でトリフルオロ酢酸5 mlを加え、室温に昇温した後1時間　した。1 M水酸化ナトリウム水溶液で中和した後、クロロホルムで抽出した。有機層を飽和食塩水で洗浄した。無水硫酸マグネシウムで乾燥後、溶媒を留去して得られた1 (ベンゾフラン 5 イル)ピペラジン910 m9のうち、500 m9を用い、以下製造例5と同様にして、1 (ベンゾフラン 5 イル) 4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン420 m9を無色結晶として得た。

製造例3 6

1 (4 アミノフェニル) 4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 355 m9のDMF 3 ml溶液に、1 クロロ 2 (2 クロロエトキシ)エタン 130 m9、ヨウ化ナトリウム 77 m9及び炭酸カリウム 249 m9を加え、100℃で一晩　した。室温まで冷却後、反応溶液を減圧下濃縮し、水を加え、クロロホルムで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、エタノール ジエチルエーテルから

結晶化して、4 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェニル)モルホリン 210 mgを黄色結晶として得た。

【００８４】

製造例３７

1 (4 アミノフェニル) 4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 211 mgのTHF 2.5 ml溶液に、メタンスルホニルクロリド 63.5 mg及びトリエチルアミン 76.8 μlを加え、室温下一晩　した。更にメタンスルホニルクロリド 79 mg及びトリエチルアミン 103 μlを2回に分けて加え、3時間室温で　した。反応液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、酢酸エチル ジイソプロピルエーテルから結晶化して、4' {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}メタンスルホンアニリド 175 mgを淡紫色結晶として得た。

製造例３８

[(4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}ベンゾイル)アミノ]酢酸エチル 233 mgに濃塩酸0.8 mlを加え、室温下一晩　した。反応液を減圧下濃縮後、2 プロパノール ジイソプロピルエーテルから結晶化して、[(4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}ベンゾイル)アミノ]酢酸 塩酸塩を　取した。　液を減圧下濃縮し、残　をヘキサンから結晶化して、[(4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}ベンゾイル) アミノ]酢酸 1水和物88 mgを淡茶褐色結晶として得た。

【００８５】

製造例３９

2.5 クロロピラジン1.51 gのNMP 7.5 ml溶液に1 (t アトキシカルボニル)ピペラジン 2.00 g及び炭酸カリウム2.00 gを加え100℃で1時間加熱　した。室温まで冷却し、水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、2.73 gの2 クロロ 5 (4 t アトキシカルボニルピペラジン 1 イル)ピラジンを得た。これを用いて以下製造例３５と同様にして、2 クロロ 5 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}ピラジンを無色結晶として得た。

製造例４０

2 クロロ 4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}ピリミジン 1水和物 460 mgのメタノール 20 ml溶液に、10%パラジウム炭素 150 mgを加え、常圧水素雰囲気下、室温で23時間　した。不溶物を　去し、溶媒を留去し得られた残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、更にアセトニトリル ジイソプロピルエーテルから再結晶して、4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}ピリミジン 83 mgを無色結晶として得た。

【００８６】

製造例４１

4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 1 (4 ヒドロキシフェニル)ピペラジン 297 mgに、[1.3]ジオキソラン 2 オン 623 mg、炭酸カリウム 147 mgを加え、100℃で1時間半　した。室温まで冷却後、反応液に水を加えさらに1M 塩酸を加えた。飽和炭酸水素ナトリウム水溶液で中和し、クロロホルムで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を留去した。残　をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、酢酸エチルから再結晶して、2 (4 {4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル}フェノキシ) エタノール 41 mgを淡黄色結晶として得た。

製造例４２

6 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)ピリジン 3 オール 213 mgのDMF 5 ml溶液に、氷冷下、(2 クロロエチル)ジメチルアミン 塩酸塩 81 mg及び60%水素化ナトリウム 43 mgを加えた。油浴温度70℃で1時間 後、水を加え酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(クロロホルム～クロロホルム メタノール)で精製して得た生成物(110 mg)をエタノールに溶解し、シュウ酸 40 mgを加えシュウ酸塩とした後、エタノールから再結晶して、1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 4 [5 (2 ジメチルアミノエトキシ) 2 ピリジル]ピペラジン 2 シュウ酸塩 81 mgを無色結晶として得た。

【００８７】

製造例４３

4 [2 (4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル) フェノキシ)エチル]ピペラジン 1 カルボン酸 t ブチル 270 mgのクロロホルム 3 ml溶液に4M 塩化水素/酢酸エチル溶液 0.427 mlを加え、2日間室温で した。さらにクロロホルム 2 ml と4M 塩化水素/酢酸エチル溶液 1 mlを加え、室温で一晩 した。反応液にエタノールを加え、粗結晶を 取し、メタノールから再結晶して、1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 4 [4 (2 ピペラジン 1 イルエトキシ)フェニル]ピペラジン 4塩酸塩 3水和物114 mgを淡黄色結晶として得た。

製造例４４

(±) trans 1 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル] 2.5 ジメチル4 (4 ニトロフェニル)ピペラジン 1.42 gのエタノール37 ml及び水13 ml混合溶液に塩化アンモニウム 0.16 gと還元鉄 1.66 gを加え、0.5時間加熱還流した。反応液をセライトを用いて 過し、 液を減圧濃縮し、得られた残 に飽和炭酸水素ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を留去した。残 をシリカゲルカラムクロマトグラフィー(クロロホルム メタノール)で精製し、得られた化合物を4M塩化水素／酢酸エチル溶液で処理し塩酸塩後、溶媒を留去した。残 を酢酸エチルで洗浄して、(±) trans 4 (4 [6 (3.4 ジメトキシフェニル) ピリジン 2 カルボニル] 2.5 ジメチルピペラジン 1 イル)アニリン 2塩酸塩 2水和物 582 mgを淡黄色結晶として得た。

製造例４５～２１７

上記製造例の方法と同様にして、後記表１～１７に示す製造例４５～２１７の化合物をそれぞれ得た。製造例１～２１７の化合物の構造及び物理化学的データを表１～１７に示す。

【００８８】

実施例５（化合物Ａのα型結晶の製造）

粗製の4 (4 (4 [6 (3.4 ジメトキシフェニル)ピリジン 2 カルボニル]ピペラジン 1 イル)フェニル)モルホリン（化合物Ａ） 5.0 gに酢酸エチル60 mlを加え、 下に還流温度付近まで加熱し溶解した。次いで、活性炭1.0 gを加え、更に 後、 過した。残 を酢酸エチル5 mlで洗浄した。 液を加熱し析出した結晶を溶解後、放冷し、30℃で終夜 し、更に冷却し0℃で4時間 した。析出した結晶を 取し、減圧乾燥して、α型結晶3.97 gを得た。

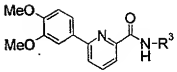
実施例６（化合物Ａのβ型結晶の製造）

粗製の化合物Ａ 2.5 gにメタノール13 ml及びアセトン8 mlを加え、 下に還流温度付近まで加熱し溶解した。次いで、活性炭0.5 gを加え、更に 後、 過した。残 をメタノール3 mlで洗浄した。 液を加熱し析出した結晶を溶解後、 しながら種晶としてα型結晶を少量加えた。 下、徐々に冷却し0℃で終夜 し析出した結晶を 取し、メタノールで洗浄後、減圧乾燥してα型結晶とβ型結晶の結晶混合物1.95 gを得た。得られた結晶混合物の1.0 gを用い、メタノール5 ml及びアセトン2 mlを加え、45℃で12時間、次いで20℃で12時間、更に1℃で12時間 した。結晶を 取し、メタノールで洗浄後、減圧乾燥して、β型結晶0.9 gを得た。

実施例7（化合物Aのβ型結晶の製造）

化合物A 380.10 gにエタノール2680 ml、酢酸エチル980 mlを加えた。　下に還流温度付近まで加熱、溶解し、熱時　過した。　紙及び　過器を酢酸エチル100 mlで洗浄し、先の　液と合した。　液を加熱し析出した結晶を溶解後、65～70℃に　しながら種晶としてβ型結晶を少量加えた。徐々に冷却後、40℃で終夜　し、更に徐々に冷却後、0℃で終夜　した。析出した結晶を　取し、エタノールで洗浄後、減圧乾燥して、β型結晶359.85 gを得た。

【表１】



Ex	Syn	R^3	Dat	Sal
4	4		NMR1: 13.41 (1H, s), 5.06 (1H, dd, J= 9.3, 7.4Hz), 3.99 (3H, s); MP: 159-161	
5	5		NMR1: 8.58 (2H, d, J=4.3 Hz), 8.11 (1H, dd, J=7.8, 1.0Hz), 3.95 (3H, s) MP: 184-187	
6	6	$-C(Ph)_2CO_2H$	NMR2: 8.03(1H,t, J=7.8 Hz), 7.12 (1H, d, J=8.4 Hz), 3.94 (3H, s); MP: 209-212	
7	7		NMR2: 10.05 (1H, s), 6.44 (1H, q, J= 9.2 Hz), 3.88 (3H, s), 3.85 (3H, s); MP: 131-133	
8	8		NMR2: 6.72 (1H, d, J= 8.8 Hz), 3.88 (3H, s), 3.84 (3H, s), 3.83 (3H, s); MP: 172-174	HCl
9	9		NMR2: 8.20 (1H, d, J=7.8 Hz), 3.91 (3H, s), 2.23-2.17 (2H,m); MP: 195-203	Fum 1.5 H_2O
10	10		NMR2: 8.19 (1H, d, J=8.3Hz), 3.92 (3H, s), 2.43(3H,s); MP: 197-201	Fum
11	11		NMR2: 7.91 (1H, d, J=7.3 Hz), 4.13 (2H, s), 3.91 (3H, s); MP: 170-172	Ox
12	12		NMR2: 8.04 (1H, t, J=7.8 Hz), 3.89 (3H, s), 2.76 (2H, m); MP: 112-116	2 Fum H_2O
13	13		NMR1: 3.99 (3H, s), 3.84 (2H, d, J= 5.8Hz), 3.52 (2H,s); MP: 120-122	
14	14		NMR2: 8.79 (1H, s), 3.90 (3H, s), 3.85 (3H, s), 3.64 (2H, s); MP: 191-192	H_2O
15	15	$-OBn$	NMR1: 7.81 (1H, dd, J=7.8, 1.0 Hz), 5.10 (2H, s), 3.94 (3H, s); MP: 111-112	
16	16	$-OH$	NMR2: 7.99(1H, t, J=7.8Hz), 7.05 (1H, d, J=8.3 Hz), 3.91 (3H, s); MP: 170-173	
17	17		NMR1: 8.11 (1H, dd, J=7.8, 1.0 Hz), 6.34 (1H, d, J=7.3Hz), 3.95 (3H, s) MP:176-179	

【００８９】

【表２】

45	2		NMR1: 7.39 (1H, d, J=7.4 Hz), 5.70 (1H, dd, J=16.1 Hz, 7.8 Hz), 3.90 (3H, s); MP: 120-122	
46	2		NMR1: 7.52 (1H, s), 4.47 (2H, s), 3.34 (3H, s); MP: 146-148	
47	2		NMR2: 8.18 (1H, d, J=7.8Hz), 3.93 (3H, s), 3.60-3.51(4H,m); MP: 163-166	Fum MeCN
48	2		NMR1: 7.61 (1H, dd, J=8.3, 2.0 Hz), 3.99 (3H, s), 3.53 (2H, s); MP: 177-179	
49	2		F:407	
50	18		NMR2: 8.05 (1H, t, J=7.8Hz), 570 (1H, d, J=8.3Hz), 3.91 (3H, s); MP: 224-226	
51	2		F: 483	
52	18		NMR2: 12.93 (1H, s), 6.46(1H, d, J=8.8Hz), 3.88 (3H, s); MP: 208-209	
53	5		F:421	
54	18		NMR2: 8.03 (1H, t, J=7.8 Hz), 3.93 (3H, s), 3.07 (1H, dd, J=16.1, 6.9 Hz); MP: 181-182	
55	5		NMR2: 5.61 (1H,d,J=7.8Hz), 3.92 (3H, s), 2.36 (6H,s); MP: 185-187	1.5 Fum
56	5		NMR2: 8.16 (1H,d,J=7.8Hz), 3.83 (6H, s), 2.28 (3H,s); MP: 206-209	2 Fum
57	5		NMR2: 8.17 (1H,d,J=7.3Hz), 4.31-4.27 (2H,m) 3.84 (6H, s); MP: 141-142	Ox
58	5		NMR2: 6.46 (1H, d, J= 8.8 Hz), 3.89 (3H, s), 3.83 (3H, s); MP: 138-139	
59	5		NMR2: 7.12 (1H, d, J= 8.3 Hz), 6.63 (1H, d, J= 7.6 Hz), 3.94 (3H, s), 3.85 (3H, s); MP: 125-126	
60	5		F: 532	

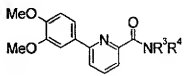
【００９０】

【表３】

61	5		NMR1: 8.10 (1H, d, J=7.9 Hz), 4.00 (3H, s), 3.06 (1H, m); MP: 112-113	
62	2		NMR1: 7.02 (1H, d, J=8.4 Hz), 4.00 (3H, s), 3.51 (2H, s)	
63	18		NMR2: 12.52 (1H,s),7.35-7.23 (5H, m), 3.93 (3H, s); MP: 237-240	
64	5		NMR1: 4.03 (3H, s), 3.70-3.68 (4H, m), 2.16-2.12 (2H,m); MP: 212-214	
65	5		NMR2: 7.85 (1H, dd, J=7.3,1.9 Hz), 4.28(2H,d,J=5.4Hz), 3.91 (3H, s); MP:170-173	Ox
66	5		NMR1: 7.92 (1H, d, J=2.0 Hz), 6.36 (1H, d, J=7.3Hz), 4.13 (3H, s); MP: 167-169	
67	25		NMR1: 7.03 (1H, d, J=8.3Hz), 3.99 (3H, s), 3.54 (2H,s); MP: 189-190	
68	10		NMR1: 8.02 (1H, dd, J=6.8, 1.9 Hz), 4.00 (3H, s), 2.14 (2H, d, J=6.9Hz); MP: 148-150	
69	1		NMR2: 8.02 (1H, m), 5.20 (1H, td, J= 8.8, 5.4 Hz), 3.93 (3H, s); MP: 169-171	Ox
70	5		NMR1: 6.98 (1H,d,J=8.8Hz), 6.40 (1H,d,J=7.9Hz), 3.95 (3H,s,); MP: 144-146	

【００９１】

【表４】



Ex	Syn	R^3	R^4	Dat	Sal
18	18		$-CH_2CO_2H$	F: 447 MP: 187-188	
19	19	$-(CH_2)_2OMe$		NMR1: 7.85 (1H, t, J=7.8 Hz), 3.94 (3H, s), 3.59 (2H, t, J=6.4 Hz); F: 385	

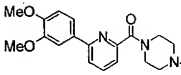
【００９２】

【表５】

71	19		−iBu	NMR2: 3.83 (3H, s), 3.06-2.98 (3H,m) 0.72 (3H,d, J= 6.8Hz); MP: 187-192	Ox
72	19			F: 468 MP: 164-166	Ox
73	19			F: 531 MP: 137-138	
74	2		$-CH_2CO_2Me$	F: 461	
75	2			NMR2(120℃): 7.50 (1H,dd, J= 6.3, 1.0Hz), 5.40(1H,m), 3.82 (3H, s); MP: 125-127	
76	19			F: 481; MP: 139-141	
77	19			F: 530; MP: 148-150	
78	21			F: 496; MP: 153-154	
79	19			EI: 513; MP: 133-134	
80	19			F: 578; MP: 161-164	
81	19 & 18			F: 552; MP: 117-120	
82	5	$-(CH_2)_2OMe$		NMR1: 7.81 (1H, m), 3.95 (3H, s), 3.68-3.83 (2H, m); F: 431	
83	5			NMR2(120℃): 7.05 (1H, d, J= 8.0 Hz), 4.61 (1H, brs), 3.83 (6H, s); F: 531	
84	5			F:529 MP:149-153	Ox 1.5 H_2O

【００９３】

【表６】



Ex	Syn	R^5	Dat	Sal
2	2	4-OMe-Ph	NMR1: 7.84 (1H, t, J=7.8 Hz), 3.96 (3H, s), 3.78 (2H, s); MP: 169-172	
3	3		NMR2: 3.85(3H,s), 3.82(3H, s), 3.13-3.16(4H,m), 2.79(6H,s); MP:136-137	2 Ox
20	20		NMR2: 8.32(1H, s), 7.90(1H, s), 3.88 (3H, s), 3.83 (3H, s); MP:160-161	
21	21	4-NH_2-Ph	NMR2: 8.28-8.30 (2H, m), 3.87 (3H, s), 3.83 (3H, s); F: 421	1.5 H_2O
22	22	4-Ac-Ph	NMR2: 4.62 (2H, br s), 3.85 (3H, s), 2.98-3.03 (4H, m); MP: 164-165	
32	32		NMR1: 8.10 (1H, d, J=6.3 Hz), 6.98 (1H, d, J=8.7 Hz), 6.43 (1H, d, J=6.3 Hz); MP: 98-100	H_2O
33	33	4-$CONH_2$-Ph	NMR2: 3.85 (3H, s), 7.03 (1H, br s), 7.68-7.79 (5H, m); MP: 237-240	
34	34		NMR2: 1.44-1.54 (2H, m), 3.85 (3H, s), 9.59 (1H, s); MP: 217-219	
35	35		NMR1: 6.97 (1H,d,J=8.3Hz), 6.69-6.71 (1H,m), 3.20-3.30 (4H,m); MP: 176-178	
36	36		NMR2: 3.69-3.73 (6H, m), 3.85 (3H, s), 6.85-6.91 (4H, m); MP: 129-130	
37	37	4-($NHSO_2Me$)-Ph	NMR2: 2.88 (3H, s), 3.82 (3H, s), 9.28 (1H, s); MP: 168-170	
38	38		NMR2: 3.82 (3H, s), 8.55 (1H, t, J=5.8 Hz), 12.50 (1H, br s); MP: 114-117	H_2O
39	39		NMR1: 8.11 (1H,d,J=1.5Hz), 6.98 (1H,d,J=8.3Hz), 3.69-3.80 (4H,m); MP: 160-162	
40	40		NMR1: 8.63 (1H, s), 8.26 (1H, d, J=6.3 Hz), 6.98 (1H, d, J=8.3 Hz); MP: 138-139	

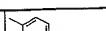
【００９４】

【表７】

41	41		NMR2: 3.65-3.72 (4H, m), 3.82 (3H, s), 4.80 (1H, t, J=5.4 Hz); MP: 111-113	
42	42		NMR1: 6.66 (1H, d, J=8.8 Hz), 3.97 (3H, s), 3.95 (3H, s), 2.91 (6H, s); MP: 144-147	2 Ox
43	43		NMR2: 3.82 (3H, s), 3.84 (3H, s), 7.68-7.72 (2H, m); MP: 155-158	4 HCl 3 H_2O
85	2	4-NMe_2-Ph	NMR1: 7.78(1H, dd, J= 8.3, 1.0 Hz), 3.96(3H, s), 2.53(3H,s); MP: 161-163	
86	5		NMR2: 3.85(3H,s), 3.82(3H,s), 3.05-3.08(4H,m), 2.79(6H,s); MP: 159-161	
87	5		NMR2: 8.36 (1H, d, J=0.9 Hz), 7.09 (1H, d, J= 8.0 Hz), 3.86 (3H, s), 3.82 (3H, s); MP: 122-124	
88	5		NMR2: 8.19 (2H, d, J= 5.9 Hz), 3.86 (3H, s), 3.82 (3H, s), 3.45-3.52 (4H, m); MP: 155-156	
89	5	2-Cl-4-OMe-Ph	NMR2: 7.15 (1H, d, J = 9.0 Hz), 7.05 (1H, d, J =3.0 Hz), 6.91 (1H, dd, J = 9.0, 3.0 Hz); MP: 155-156	
90	5	4-CN-Ph	NMR2: 8.06(1H,d,J=7.8Hz), 3.85 (3H,s), 3.47-3.54(4H,m); MP: 146-148	
91	5	4-CO_2Et-Ph	NMR2: 3.86(3H, s), 3.45-3.51(4H, m), 1.29(3H, t,J=7.3Hz); MP: 112-114	
92	10	-CH_2-(2-OH-3-OMe-Ph)	NMR1: 7.54 (1H,dd, J=8.3, 2.0 Hz), 3.78 (2H, s), 2.76-2.66 (4H,m); MP: 155-158	
93	10		NMR1: 6.97 (1H,d,J=8.3Hz), 3.98 (3H, s), 2.09 (3H, s); MP: 120-122	
94	5& 20		NMR2: 3.86 (3H, s), 3.83 (3H, s), 2.75 (3H, d, J= 4.4 Hz); F: 530	2 HCl 2 H_2O
95	5& 20		NMR2: 8.67 (1H, t, d= 5.4 Hz), 3.86 (3H, s), 3.83 (3H, s), 2.82 (3H, s), 2.80 (3H, s); F: 518	2 HCl 2 H_2O
96	3	4-NHAc-Ph	NMR2: 1.99 (3H, s), 3.85 (3H, s), 9.71 (1H, s); MP: 201-203	
97	3	4-(NHCO-Ph)-Ph	NMR2: 3.82 (3H, s), 6.98 (2H, d, J=9.3 Hz), 10.07 (1H, s); MP: 169-171	
98	37	4-($NHSO_2$-Ph)-Ph	NMR2: 3.82 (6H, s), 6.80-6.85 (2H, m), 9.85 (1H, s); MP: 187-189	

【００９５】

【表８】

99	5		NMR2: 1.19 (6H, t, J=7.4 Hz), 2.72-2.75 (2H, m), 10.02 (1H, s); MP: 131-134	Ox
100	18	4-CO_2H-Ph	NMR2: 3.86 (3H, s), 6.99 (2H, d, J=9.3 Hz), 12.32 (1H, br s); MP: 209-211	
101	5	4-OH-Ph	NMR2: 3.84 (3H, s), 6.82 (2H, d, J=8.8 Hz), 8.88 (1H, s); MP: 177-179	
102	5	4-NO_2-Ph	NMR2: 3.86 (3H, s), 7.04 (2H, d, J=9.2 Hz), 8.06-8.10 (3H, m); MP: 142-144	
103	5		NMR1: 7.05 (1H, d, J=9.8 Hz), 6.98 (1H, d, J=8.3 Hz), 6.89 (1H, d, J=9.3 Hz), 4.04 (3H, s); MP: 171-172	
104	5		NMR1: 7.58 (1H, dd, J=8.3, 2.0 Hz), 6.98 (1H, d, J=8.3 Hz), 3.85 (3H, s), 3.40-3.28 (4H, m); MP: 158-159	
105	5		NMR1: 7.01 (1H,m), 6.98 (1H,d, J=8.3Hz), 3.56-3.61 (4H,m); MP: 141-143	
106	5	3-Cl-4-OMe-Ph	NMR1: 6.98 (1H,d,J=8.8Hz), 3.86 (3H,s), 3.13-3.24 (4H,m); MP: 158-159	
107	5		NMR1: 7.57 (1H, dd, J=8.3, 2.4 Hz), 6.94 (1H, d, J=9.7 Hz), 3.86-3.74 (4H, m); MP: 161	
108	5	4-Ac-3-CF_3-Ph	NMR2: 2.52 (3H, s), 3.82 (3H, s), 7.83 (1H, d, J=8.7 Hz); MP: 142-143	
109	5	3-F-4-OMe-Ph	NMR1: 6.97 (1H,d,J=8.3Hz), 3.85 (3H,s), 3.13-3.24 (4H,m); MP: 155-156	
110	5		NMR1: 6.97 (1H, d, J=8.7 Hz), 6.71 (1H, d, J=8.8Hz), 3.90 (3H, s), 3.24-3.11 (4H, m); MP: 179-181	
111	5		NMR1: 8.74 (1H, dd, J=4.4, 1.5 Hz), 3.97 (3H, s), 3.95 (3H, s), 3.50-3.38 (4H, m); MP: 144-145	
112	5		NMR2: 3.85 (3H, s), 4.03-4.21 (4H, m), 6.46-6.49 (2H, m); MP: 187-188	
113	5	4-SO_2NH_2-Ph	NMR2: 3.85 (3H, s), 7.05-7.10 (5H, m), 7.65 (2H, d, J=9.3 Hz); MP: 213-214	
114	3	4-Ac-3-OH-Ph	NMR2: 2.49 (3H, s), 3.86 (3H, s), 12.76 (1H, s); MP: 135-137	

【００９６】

【表９】

115	5		NMR1: 8.43 (1H, d, J=1.9 Hz), 3.90 (3H, s), 3.87-3.82 (4H, m); MP: 162-163	
116	18		NMR2: 3.84 (3H, s), 4.58 (2H, s), 12.90 (1H, br s); MP: 143-145	H_2O
117	5		NMR1: 9.04 (1H, d, J=2.9 Hz), 6.98 (1H, d, J=8.3 Hz), 6.61 (1H, d, J=9.2 Hz); MP: 183-184	
118	3		NMR2: 2.56-2.59 (4H, m), 3.59 (3H, s), 9.78 (1H, s); MP: 140-142	
119	5		NMR1: 6.52 (1H, d, J=8.3 Hz), 3.99 (3H, s), 3.95 (3H, s), 3.75-3.68 (4H, m); MP: 107-109	
120	5		NMR1: 8.15 (1H,d,J=2.4Hz), 6.97 (1H,d,J=8.3Hz), 3.55-3.64 (4H,m); MP: 140-142	
121	5		NMR1: 7.09-7.13 (1H,m), 6.98 (1H,d, J=8.3Hz), 3.79-3.83 (4H,m); MP: 172-173	
122	27		NMR2: 1.71-1.76 (4H, m), 3.82 (3H, s), 4.26 (2H, t, J=4.9 Hz); MP: 161-165	1.5 Ox
123	35	2-Cl-4-Ac-Ph	NMR1: 7.04 (1H,d,J=8.3Hz), 6.97 (1H,d,J=8.3Hz), 2.56 (3H,s); MP: 164-165	
124	18		NMR2: 12.06 (1H,s), 7.53 (1H,d, J=7.4Hz), 2.73 (2H,t,J=7.6Hz); MP: 169-171	
125	18		NMR2: 12.56 (1H, br), 8.65 (1H, d, J=2.0 Hz), 7.09 (1H, d, J=8.3 Hz); MP: 220-222	
126	5		NMR1: 8.81 (1H, d, J=2.5 Hz), 3.98 (3H, s), 3.95 (3H, s), 3.88 (3H, s); MP: 157-159	
127	5		NMR2: 1.20 (3H, t, J=6.9 Hz), 3.82 (3H, s), 8.63-8.66 (1H, m); MP: 83-85	
128	18		NMR2: 1.59-1.73 (4H, m), 3.85 (3H, s), 12.02 (1H, s); MP: 79-81	H_2O
129	18		NMR2: 2.32-2.39 (2H, m), 3.85 (3H, s), 12.11 (1H, br s); MP: 123-125	

【００９７】

【表１０】

130	35		NMR1: 7.98 (1H,s), 6.98 (1H,d, J=8.3Hz), 3.28-3.41 (4H,m); MP: 151-153	
131	33		NMR2: 7.78 (1H, br), 7.16 (1H, br), 6.88 (1H, d, J=8.8 Hz), 3.87 (3H, s); MP: 243-244	
132	18		NMR2: 1.36-1.44 (2H, m), 3.85 (3H, s), 11.98 (1H, s); MP: 91-93	H_2O
133	3	4-CH_2OH-Ph	NMR2: 3.82 (3H, s), 4.39 (2H, d, J=5.9 Hz), 4.96 (1H, t, J=5.9 Hz); MP: 150-152	
134	5		NMR1: 8.41 (1H, s), 6.98 (1H, d, J=8.3 Hz), 3.98 (3H, s); MP: 119-120	
135	27	4-Ac-3-OMe-Ph	NMR2: 2.44 (3H, s), 3.88 (3H, s), 6.53 (1H, s); MP: 117-118	0.5 H_2O
136	5		NMR2: 4.09 (2H, S), 10.23 (1H, s), 16.22 (1H, br); MP: 217-219	0.5 H_2O
137	5		NMR1: 6.55 (1H, d, J=8.3 Hz), 4.00 (3H, s), 3.95 (3H, s), 3.75-3.66 (4H, m); MP: 144-145	
138	5		NMR1: 7.32 (1H, d, J=8.8 Hz), 3.96 (3H, s), 3.94 (3H, s), 3.31-3.18 (4H, m); MP: 193-194	
139	5		NMR1: 8.21 (1H, d, J=2.4 Hz), 3.98 (3H, s), 3.95 (3H, s), 3.70-3.64 (4H, m); MP: 127-128	
140	18		NMR2: 3.85 (3H, s), 9.75 (1H, s), 12.09 (1H, br); MP: 167-170	
141	18		NMR2: 1.28-1.43 (4H, m), 3.85 (3H, s), 11.97 (1H, br s); MP: 102-109	H_2O
142	5		NMR2: 4.53 (1H, t, J=4.9 Hz), 3.88 (3H, s), 3.83 (3H, s), 3.31-3.18 (4H, m), 2.81 (6H, s); MP: 180-181	1.5 Ox
143	5	2-OMe-Ph	NMR2: 3.79 (3H, s), 3.85 (3H, s), 6.87-7.02 (4H, m); MP: 162-163	
144	5	3-OMe-Ph	NMR2: 3.72 (3H, s), 3.85 (3H, s), 6.48-6.50 (1H, m); MP: 180-181	
145	18		NMR2: 1.91 (2H, quintet, J=6.8 Hz), 3.85 (3H, s), 12.12 (1H, br s); MP: 109-112	

【００９８】

【表１１】

146	18		NMR2: 1.60-1.75 (4H, m), 3.85 (3H, s), 12.03 (1H, br); MP: 119-120	H_2O
147	18		NMR2: 1.37-1.45 (2H, m), 3.85 (3H, s), 11.98 (1H, s); MP: 97-99	
148	18		NMR2: 11.97 (1H,s), 7.52 (1H,d, J=7.4Hz), 2.22 (2H,t,J=6.9Hz); MP: 159-161	
149	18		NMR2: 6.13 (1H, d, J=7.3 Hz), 3.87 (3H, s), 3.83 (3H, s), 2.21 (1H, t, J=7.6 Hz); MP: 182-185	
150	18		NMR1: 7.93 (1H, d, J=2.9 Hz), 3.97 (3H, s), 3.94 (3H, s), 2.57 (1H, t, J=7.1 Hz); MP: 122-124	
151	27		NMR2: 1.22 (6H, t, J=7.3 Hz), 3.45-3.48 (2H, m), 3.82 (3H, s); MP: 97-99	Ox H_2O
152	18		NMR1: 6.97 (1H,d,J=8.8Hz), 6.63 (1H,d,J=8.8Hz), 2.61 (2H,t,J=7.3Hz); MP: 190-191	
153	18		NMR2: 1.97 (2H, quintet, J=6.8 Hz), 3.82 (3H, s), 12.11 (1H, s); MP: 133-134	
154	18		NMR2: 1.66-1.80 (4H, m), 3.82 (3H, s), 12.01 (1H, s); MP: 176-178	
155	18		NMR2: 1.42-1.50 (2H, m), 3.82 (3H, s), 12.11 (1H, br); MP: 129-130	
156	18		NMR1: 6.96 (1H,d,J=8.3Hz), 6.62 (1H,d,J=8.8Hz), 2.36 (2H,t,J=6.8Hz); MP: 158-160	
157	33	4-(CONHMe)-Ph	NMR2: 2.75 (3H, d, J=3.5 Hz), 3.85 (3H, s), 8.13-8.18 (1H, m); MP: 140-141	
158	18		NMR1: 7.14 (1H, d, J=8.8 Hz), 4.00 (3H, s), 3.95 (3H, s), 2.65 (1H, t, J=7.1 Hz); MP: 189-191	
159	36		NMR2: 1.45-1.52 (2H, m), 3.85 (3H, s), 6.83-6.88 (4H, m); MP: 135-137	0.5 H_2O

【００９９】

【表１２】

160	5	4-NEt_2-Ph	NMR2: 1.30 (6H, t, J=7.0 Hz), 3.23 (4H, q, J=7.0 Hz), 3.82 (3H, s); MP: 84-87	
161	33	4-($CONMe_2$)-Ph	NMR2: 2.95 (6H, s), 3.82 (3H, s), 7.32 (2H, d, J=8.3 Hz); MP: 81-83	H_2O
162	27		NMR2: 2.80 (6H, br s), 3.85 (3H, s), 6.85-6.95 (4H, m); F: 505	Ox H_2O
163	27		NMR2: 2.71 (3H, s), 3.82 (3H, s), 4.04 (2H, t, J=5.3 Hz); MP: 183 (dec)	Ox H_2O
164	27		NMR2: 1.33-1.42 (2H, m), 3.82 (3H, s), 4.52 (1H, d, J=3.9 Hz); MP: 143-144	
165	5		NMR2: 6.80 (1H, d, J=8.8 Hz), 3.85 (3H, s), 3.82 (3H, s), 2.78 (6H, s); MP: 114-115	Ox H_2O
166	42		NMR1: 3.97 (3H, s), 3.95 (3H, s), 3.59-3.54 (4H, m), 1.07 (6H, t, J=7.2 Hz); F: 520	HCl 2 H_2O
167	42		NMR2: 7.28 (1H, d, J=1.9 Hz), 3.87 (3H, s), 3.82 (3H, s), 2.80 (6H, s); MP: 195-198	Ox 0.5 H_2O
168	42		NMR2: 6.97 (1H, d, J=8.6 Hz), 4.71 (2H, s), 1.31 (3H, t, J=7.3 Hz); MP: 140-142	
169	18		NMR2: 4.74 (2H, s), 3.86 (3H, s), 3.82 (3H, s), 3.35-3.25 (4H, m); MP: 198-200	
170	18		NMR1: 6.97 (1H, d, J=8.3 Hz), 3.96 (3H, s), 3.94 (3H, s), 2.63 (2H, t, J=7.4 Hz); MP: 153-154	
171	42		NMR2: 7.35 (1H, dd, J=9.0, 3.4 Hz), 4.19 (2H, t, J=5.4 Hz), 2.78-2.76 (4H, m); MP: 163-165	Ox 0.5 H_2O
172	27		NMR2: 3.82 (3H, s), 5.09 (2H, s), 6.94 (4H, s); MP: 137-139	
173	27		NMR2: 1.12-1.23 (2H, m), 3.82 (3H, s), 6.90-6.97 (4H, m); MP: 202-205	Ox 0.5 H_2O

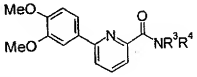
【０１００】

【表１３】

174	27		NMR2: 2.15 (1H, br), 3.82 (3H, s), 4.23 (2H, t, J=5.3 Hz), ; F: 533	2 Ox
175	27		NMR2: 3.30 (3H, s), 3.82 (3H, s), 4.00-4.02 (2H, m), ; MP: 104-108	
176	27		NMR2: 3.82 (3H, s), 5.12 (2H, s), 6.93 (4H, s); MP: 140-142	
177	42		NMR2: 7.37 (1H, dd, J=8.8, 2.4 Hz), 4.28 (2H, t, J=5.4 Hz), 3.85 (3H, s), 3.82 (3H, s); MP: 167-173	Ox 0.5 H_2O
178	18		NMR2: 8.76 (1H, d, J=8.8 Hz), 3.86 (3H, s), 3.83 (3H, s), 2.91 (3H, s); MP: 135-140	2 HCl 2 H_2O
179	27		NMR2: 5.06 (2H, s), 6.94 (4H, s), 8.28 (1H, br s); MP: 147-148	
180	27		NMR2: 3.82 (3H, s), 5.05 (2H, s), 8.19-8.23 (2H, m); MP: 182-183	
181	27		NMR2: 3.82 (3H, s), 4.13-4.16 (2H, m), 6.88-6.95 (4H, m); MP: 109-111	1.5 Ox
182	27		NMR2: 2.15-2.23 (2H, m), 3.82 (3H, s), 6.96-7.02 (2H, m); MP: 213-217	2 HCl 1.5 H_2O
183	27		NMR2: 3.28 (6H, s), 3.82 (3H, s), 4.16 (2H, t, J=5.4 Hz); F: 579	2 Ox
184	27		NMR2: 3.82 (3H, s), 4.00-4.05 (2H, m), 6.86 (2H, d, J=8.8 Hz); MP: 106-109	2 Ox 2 H_2O
185	18		NMR2: 1.93 (2H, t, J=6.9 Hz), 3.85 (3H, s), 5.51 (1H, br); MP: 165-170	3 HCl
186	18		NMR2: 2.79 (3H, br s), 3.85 (3H, s), 12.06 (1H, s); MP: 138-139	H_2O

【０１０１】

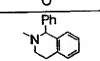
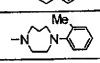
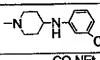
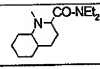
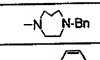
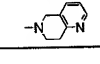
【表１４】



Ex	Syn	NR^3R^4	Dat	Sal
1	1		NMR2: 7.63-7.73 (2H, m), 4.52 (1H, m), 2.77-3.33 (4H, m); MP: 180-181	0.5 Fum
44	44		NMR2: 8.09-7.93 (2H, m), 7.76-7.64 (2H, m), 1.02 (3H, d, J=6.3 Hz); MP: 205-210	2 HCl 2 H_2O
187	5		NMR2: 7.08 (1H, dd, J = 8.3, 3.0 Hz), 6.98-6.94 (2H, m), 4.08-4.01 (1H, m); MP: 147-148	
188	1		NMR2: 7.93 (1H, t, J=7.8 Hz), 3.86 (3H, s), 2.09 (1H, m) MP: 173-176 (dec.)	Fum
189	3		NMR2: 1.10-1.13 (3H, m), 1.31-1.37 (3H, m), 2.44 (3H, s); MP: 134-135	
190	18		NMR2: 0.96-0.99 (3H, m), 3.82-3.84 (6H, m), 7.05-7.11 (2H, m); MP: 160-162	
191	18		NMR2: 0.95-0.98 (3H, m), 1.93-1.96 (2H, m), 3.81-3.84 (6H, m); MP: 124-127	3 H_2O
192	5		NMR2: 8.50 (1H, d, J=2.0 Hz), 3.83 (3H, s), 3.82 (3H, s), 1.33-1.14 (6H, m); MP: 93-99	
193	36		NMR1: 7.87-7.66 (3H, m), 3.06-3.03 (4H, m), 1.12-1.04 (3H, m); MP: 167-172	
194	21		NMR2: 3.81 (3H, s), 5.24 (2H, s), 8.58-8.60 (2H, m); MP: 171-174	

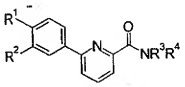
【０１０２】

【表１５】

195	2		NMR1: 7.86 (1H, t, J=7.8 Hz), 4.71-4.65 (1H,m), 3.91(3H,s); MP: 220-223	
196	2		NMR1: 6.89 (1H, d, J=8.4Hz), 3.96 (3H, s), 3.63(1H,s); MP: 162-164	
197	2		NMR1: 7.73 (1H, m), 3.92 (3H, s), 3.29 (2H, m), F: 432	
198	5		NMR1: 7.74 (1H, dd, J=8.3, 1.0 Hz), 4.68 (1H,m), 3.94 (3H,s); MP: 144-146	
199	5		NMR1: 7.78(1H, dd, J= 7.8, 0.9 Hz), 3.95 (3H, s), 1.16 (3H, t, J=6.8Hz); F: 480	
200	5		NMR1: 7.71 (1H, m), 3.94 (3H, s), 2.86 (1H, m); F: 432	
201	5		NMR2: 3.01-3.12 (2H, m), 4.85-4.89 (2H, m), 8.39-8.42 (1H, m); MP: 77-79	

【０１０３】

【表１６】



Ex	Syn	R^1, R^2	NR^3R^4	Dat	Sal
23	23			NMR1: 7.77(1H, dd, J=7.8, 1.0 Hz), 5.76(1H, q, J=8.3 Hz), 4.29(4H, s); MP:115-117	
24	24			NMR2: 8.00 (1H, dd, J= 7.8, 1.0Hz), 5.59(1H, q, J=8.3Hz), 2.42 (6H, s); MP: 155-157	Fum
25	25			NMR1: 7.80 (1H, dd, J= 7.8, 1.0Hz), 5.71(1H, q, J=7.8Hz), 5.20 (2H, s); MP: 129-131	
26	26			NMR2: 12.95 (0.4H, brs), 5.60 (1H, q, J= 8.5 Hz), 3.83 (3H, s); MP: 184-185	
27	27			NMR2: 5.59 (1H, q, J= 8.3 Hz), 3.81 (3H, s), 2.20 (6H, s); MP: 121-122	
28	28			NMR2: 7.13 (1H, d, J= 8.8 Hz), 5.60 (1H, q, J= 8.3 Hz), 3.88 (3H, s), 2.11 (3H, s); MP: 175-176	
29	29			NMR1: 7.91 (1H, t, J=7.8 Hz), 5.73 (1H, q, J=8.3 Hz), 2.01 (2H, q, J=8.3 Hz); F: 371	
30	30			NMR2: 5.56 (1H, q, J= 8.0 Hz), 3.82 (3H, s), 2.76 (3H, s); F: 374	Ox H_2O
31	31			NMR2: 5.61 (1H, q, J= 8.3 Hz), 4.01 (3H, s), 3.33 (6H, s); F: 388	HCl 2 H_2O
202	23			NMR2: 9.02 (1H, d, J= 8.8 Hz), 5.64 (1H, q, J= 8.8 Hz), 3.81 (3H, s); F: 345	HCl
203	23			NMR2: 9.05 (1H, d, J= 8.8 Hz), 5.63 (1H, dt, J= 8.3, 8.8 Hz), 3.83 (3H, s); F: 345	

【０１０４】

【表１７】

204	23			NMR2: 9.11(1H, d, J=9.2Hz), 6.08 (2H, s), 5.65 (1H, dt, J=8.8, 9.2Hz); MP: 145-148	
205	5			F: 451	
206	5			F: 451	
207	5			NMR1: 7.91 (1H, t, J=7.8 Hz), 5.76 (1H, q, J=8.3 Hz), 2.32 (3H, s); F: 343	
208	5			FN: 388	
209	5			F: 500 MP: 154-157	Ox H_2O
210	5			NMR1: 7.76 (1H, dd, J= 8.3, 1.0Hz), 2.53 (3H, s), 0.32-0.38 (2H, m); MP: 142-144	
211	5			NMR1: 8.08 (1H, d, J= 2.5 Hz), 7.03 (1H, d, J=8.8Hz), 2.53 (3H, s); MP: 168-170	
212	5			NMR1: 7.07 (1H, d, J= 8.8 Hz), 6.62 (1H, t, J=74.8Hz), 2.54 (3H, s); MP: 160-162	
213	5			F: 529 MP: 168-170	
214	29			F: 361	
215	29			NMR1: 6.91 (1H, d, J= 8.2 Hz), 5.71(1H,s), 3.93 (3H, s)	
216	29			F: 360	
217	25			NMR2: 8.64(1H, d, J=1.5Hz), 3.93 (3H, s), 2.04-1.94(1H,m) MP: 137-138	

【図面の簡単な説明】

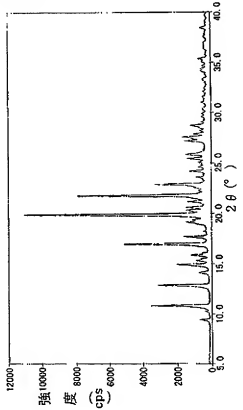
【０１０５】

【図１】４（４［６（３．４ ジメトキシフェニル）ピリジン ２ カルボニル］ピペラジン １ イル）フェニル）モルホリンのα型結晶の粉末X線回折図。

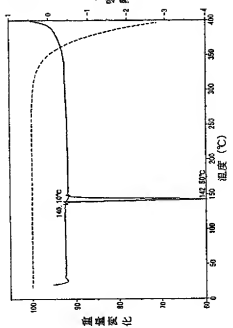
【図２】４（４［６（３．４ ジメトキシフェニル）ピリジン ２ カルボニル］ピペラジン １ イ

ル}フェニル)モルホリンのα型結晶の熱分析図。
【図３】４-(４-{４-[６-(３,４-ジメトキシフェニル)ピリジン-２-カルボニル]ピペラジン-１-イル}フェニル)モルホリンのβ型結晶の粉末X線回折図。
【図４】４-(４-{４-[６-(３,４-ジメトキシフェニル)ピリジン-２-カルボニル]ピペラジン-１-イル}フェニル)モルホリンのβ型結晶の熱分析図。

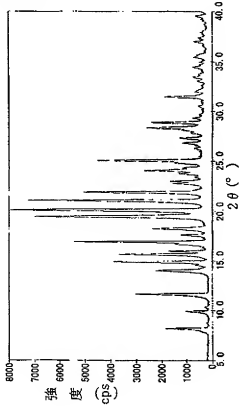
【図１】



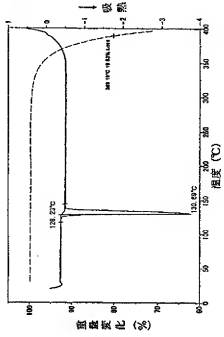
【図２】



【図３】



【図４】



フロントページの続き

(51)Int.Cl.[7]	F I	テーマコード（参考）
A61K 31/4523	A61K 31/4523	
A61K 31/4545	A61K 31/4545	
A61K 31/4725	A61K 31/4725	
A61K 31/496	A61K 31/496	
A61K 31/497	A61K 31/497	
A61K 31/501	A61K 31/501	
A61K 31/5377	A61K 31/5377	
A61K 31/55	A61K 31/55	
A61P 11/00	A61P 11/00	
A61P 11/06	A61P 11/06	
A61P 43/00	A61P 43/00　111	
// C07D 213/89	C07D 213/89	
C07D 401/12	C07D 401/12	
C07D 401/14	C07D 401/14	
C07D 405/04	C07D 405/04	
C07D 405/12	C07D 405/12	
C07D 409/12	C07D 409/12	
C07D 413/12	C07D 413/12	
C07D 417/12	C07D 417/12	
C07D 471/04	C07D 471/04　112Z	
C07M 7:00	C07M 7:00	

(72)発明者　貝沢　弘行
茨城県つくば市御幸が丘　21　山之内製薬株式会社内
(72)発明者　宅和　如文
茨城県つくば市御幸が丘　21　山之内製薬株式会社内
(72)発明者　塚本　一成
茨城県つくば市御幸が丘　21　山之内製薬株式会社内
(72)発明者　瀬尾　竜志
茨城県つくば市御幸が丘　21　山之内製薬株式会社内
(72)発明者　八尋　清
茨城県つくば市御幸が丘　21　山之内製薬株式会社内
(72)発明者　小林　幹
茨城県つくば市御幸が丘　21　山之内製薬株式会社内
(72)発明者　竹内　誠
茨城県つくば市御幸が丘　21　山之内製薬株式会社内
(72)発明者　吉田　信也
茨城県高萩市大字赤浜字松久保　160－2　山之内製薬株式会社内
(72)発明者　中村　はるか
茨城県つくば市御幸が丘　21　山之内製薬株式会社内

Fターム(参考) 4C055 AA01 AA17 BA01 BA03 BA16 BA58 BB08 BB10 CA01 DA01 DA28 DB08
4C063 AA01 BB01 BB09 CC12 CC14 CC29 CC34 CC41 CC62 CC76 CC82 CC92 DD10 DD12 EE01
4C065 AA05 BB09 CC01 DD02 EE02 HH01 JJ01 KK01 LL01 PP12
4C086 AA01 AA02 AA03 BC21 BC28 BC31 BC87 BC42 BC48 BC50 BC60 BC84 GA02 GA07 GA08 GA10 GA15 GA16 MA01 MA04

MA13 MA17 MA23 MA31 MA35 MA37 MA41 MA43 MA52 MA55
MA59 MA63 MA66 NA14 NA15 ZA59 ZC20

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 2004-203871

(43)Date of publication of application : 22.07.2004

(51)Int.Cl.

C07D213/81
A61K 31/4375
A61K 31/4418
A61K 31/4439
A61K 31/444
A61K 31/4523
A61K 31/4545
A61K 31/4725
A61K 31/496
A61K 31/497
A61K 31/501
A61K 31/5377
A61K 31/55
A61P 11/00
A61P 11/06
A61P 43/00
// C07D213/89
C07D401/12
C07D401/14
C07D405/04
C07D405/12
C07D409/12
C07D413/12
C07D417/12
C07D471/04
C07M 7:00

(21)Application number : 2003-414006

(22)Date of filing : 12.12.2003

(71)Applicant : YAMANOUCHI PHARMACEUT CO LTD

(72)Inventor : IWATA MASAHIRO
KONO NORIYUKI
KAIZAWA HIROYUKI
TAKUWA TOMOFUMI
TSUKAMOTO KAZUNARI
SEO TATSUSHI
YAHIRO KIYOSHI
KOBAYASHI MIKI
TAKEUCHI MAKOTO
YOSHIDA SHINYA
NAKAMURA HARUKA

(30)Priority

Priority number : 2002361550 Priority date : 13.12.2002 Priority country : JP

(54) MEDICINAL COMPOSITION

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a medicinal composition useful for preventing and treating respiratory diseases associated with 4-type phosphodiesterase, especially, bronchial asthma, chronic obstructive pulmonary disease and the like.

SOLUTION: A pyridine derivative or its salt having each of a phenyl which may be substituted with an alkoxy or the like at 6 position, and an N-containing heterocycle-carbonyl group bonded at 2-position with an N-substituted carbamoyl group or N-atom, is investigated to have strong and selective inhibition action to the 4-type phosphodiesterase and found to be useful as a medicinal agent.

JAPANESE [JP,2004-203871,A]

CLAIMS DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART EFFECT OF THE INVENTION TECHNICAL PROBLEM MEANS EXAMPLE DESCRIPTION OF DRAWINGS DRAWINGS

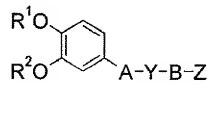
[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[Field of the Invention]
[0001]
This invention relates to the medicine which makes a phenylpyridine derivative an active principle, especially 4 type phosphodiesterase (PDE4) inhibitor.
[Background of the Invention]
[0002]
The asthma considered as the reversible blockade of a respiratory tract so far became as [regard / now / as a disease characterized by the respiratory tract irritation and airway obstruction based on the chronic respiratory tract inflammation in which many inflammatory cells participate]. The increase of the patient number is being enhanced until now, and continuing to increase further is expected.
Inhalation steroid medicine is used as an antiinflammatory drug, and xanthine derivatives, such as beta stimulants, such as procaterol, and aminophylline, and theophylline, are mainly used for the asthmatic therapy as a bronchodilator now.
Although inhalation steroid medicine has extensive anti-inflammatory activity and the usefulness as asthma preparation is high, The suitable inhalation method's needing to be taught, existence of the asthmatic of steroid resistance, etc. are pointed out (ASTHMA 13-1, 69-73 (2000), internal medicine 81, and 485-490 (1998)).
A bronchodilator activates the adenylate cyclase which is a production enzyme of intracellular adenosine 3',5'-cyclic 1 phosphoric acid (cAMP) in an airway smooth muscle, Or by checking the phosphodiesterase (PDE) which is a dialytic ferment of cAMP, intracellular cAMP concentration is raised and the remission of the contraction of an airway smooth muscle is carried out (internal medicine 69 and 207-214 (1992)). it is known that the rise of intracellular cAMP concentration will cause control of contraction in an airway smooth muscle (Clin. Exp. Allergy and 22,337-344 (1992).) It is effective in an improvement of Drugs of the Future, 17, 799-807 (1992), and the shape of asthma.
however, the thing (J. Cyclic Nucleotide and Protein Phosphorylation Res., 10, and 551-564 (1985).) for which a xanthine derivative reveals systemic side effects, such as a blood pressure fall and a strong heart operation J. If Pharmacol. Exp. Ther., 257, 741-747 (1991), and beta stimulant tend to produce hyposensitization and the amount used increases, producing side effects, such as a finger tremor and palpitation, is known.
[0003]
On the other hand, a chronic obstructive pulmonary disease (COPD) is a respiratory illness characterized by the air current restrictions relevant to an unusual inflammatory response which are not reversible.
Now, it is supposed that it is the 4th place of the cause of death in the world (2000). (Executive

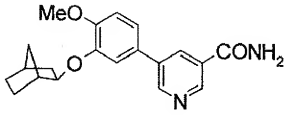
summary. Global Initiative for Chronic Obstructive Lung Disease (GOLD))
As pharmacotherapy to COPD, a bronchodilator called xanthine derivatives, such as beta stimulant, an anticholinergic drug, aminophylline, and theophylline, is generally used like asthma now. Since it attracts attention that existence of the chronic inflammation in a respiratory tract is participating in obstructive impairment greatly also in COPD, inhalation steroid medicine is also used, but. The continuous therapy by inhalation steroid FEV1 of a COPD patient. not improving the long-term fall of (forced expiratory volume in one second) is reported (N. Engl. J. Med. 340 and 1948-53 (1999).) It is anxious for Lancet 353, 1819-23 (1999), BMJ 320, 1297-303 (2000), N. Engl. J. Med. 343, 1902-9 (2000), and the antiinflammatory drug that can improve the symptoms of COPD.
[0004]
PDE was classified into seven families of PDE 1-7 at least, and it has been solved that distribution or a function has a difference, respectively (Prog. Nucleic Acid Res. Mol. Biol. 63 and 1-38 (1999)). Especially PDE4 decomposes cAMP specifically, without acting on guanosine 3',5'-cyclic 1 phosphoric acid (cGMP) also in a nucleotide.
The existence is accepted by both an airway smooth muscle and infiltrating cells.

As opposed to the eosinophil leukocytic infiltrate by an antigen and a platelet activating factor, [in / in PDE4 inhibitor / a guinea pig] Depressant action is shown (Eur. J. Pharmacol., 255, and 253-256 (1994)), What (Br. J. Pharmacol., 115, 39-47 (1995)) isolation of the obstacle nature protein (MBP, ECP) from eosinophile leucocyte is controlled for is reported. Furthermore, depressant action is shown to contraction of the airway smooth muscle by the quality of shrink material (histamine, a mesa choline, LTD_4) (Br. J. Pharmacol., 113, and 1423-1431 (1994)), Production of IL-4 which is cytokine said to participate in asthma deeply is checked (J. Invest. Dermatol., 100, and 681-684 (1993)), Depressant action is revealed to sthenia of the blood vessel permeability in a respiratory tract (Fundam. Clin. Pharmacol., 6, 247-249 (1992)), It is reported that depressant action is shown to a respiratory tract anaphylaxis (Eur. J. Pharmacol., 275, 75-82 (1995)). Therefore, PDE4 inhibitor is expected as an asthmatic treating agent.
Furthermore, having permeation depressant action to the neutrophil leucocyte it is supposed that is participated in the respiratory tract inflammation in COPD (Pulm. Pharmacol. Ther. 2001 Mar; 14(2):157-164) is reported by PDE4 inhibitor, and again, Also in the clinical trial, it is shown that a COPD patient's respiratory function can be improved (Clin. Exp. Allergy. 1999 Jun; 29 Suppl 2:99-109), and PDE4 inhibitor is expected also as a COPD remedy.
[0005]
The following compound is indicated by the patent documents 1 as a compound which has PDE4 inhibiting activity.
[Formula 2]

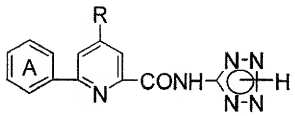


[A, Y, and B among a formula the pyridine ring etc. in which Z may be replaced by R^3 in combination etc., R^3 means $CONR^4R^5$ etc. and R^4 H, The phenyl which may be replaced with C_{1-6} alkyl, C_{1-4} alkyl, or halogen, $CH(R^7)$ CO_2R^6, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl or C_{2-5} alkylene dialkylamino (the carbon number of the dialkylamino part concerned is five or less pieces at all), R^5 H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, phenyl, pyridyl, pyrimidyl,

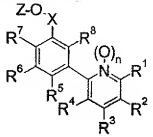
Thiazolyl, oxazolyl or R^4, and R^5 with the nitrogen atom to combine C_{1-4} alkyl of 1 thru/or 2 (1), As the saturation or the unsaturation 5 which may be replaced by the basis chosen from CO_2R^7, $CONH_2$, $CON(CH_3)_2$, oxo, OH, NH_2, and $N(CH_3)_2$ - 6 member heterocycle, and a (2) ring atom, further O, S, The saturation which has one hetero atom chosen from N (H), N (CH_3), N ($COCH_3$), or N (CH_2 Ph), unsaturation 6 member heterocycle, or the quinoline ring which may be replaced with (3) fluoride is shown.]
However, although a phenylpyridinecarboxamide derivative is included in the extensive claim of the gazette concerned, the compound which has a statement concretely is only the following 5-phenylpyridine- 3-carboxamide.
[Formula 3]



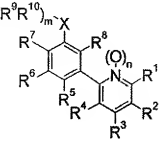
[0006]
It is indicated by the patent documents 2 as a 6-phenylpyridine- 2-carboxamide derivative that the following compound has an antiallergic action.
[Formula 4]



(R shows among a formula the phenyl group which has a substituent as which A is chosen from phenyl, halogen, low-grade alkyl, and low-grade alkoxy ** nitro and OH in hydrogen, halogen, and low-grade alkoxy ** 1-3.)
However, there is no statement about the PDE4 inhibiting activity of the compound concerned.
[0007]
Although the following phenylpyridinecarboxamide derivative which has a herbicidal action and a vegetable drying effect in the patent documents 3 and the patent documents 4 is indicated, neither an indication nor suggestion is about PDE4 inhibitory action.
[Formula 5]



,

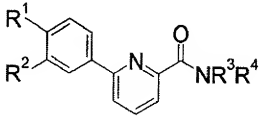


(R^1 shows $CONH_2$, CONH (C_{1-4} alkyl), $CON(C_{1-4}$ alkyl) $_2$, etc. among a formula.) Others are concerned referring to the gazette.

[0008]

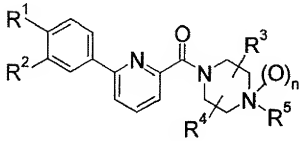
As a phenylpyridinecarboxamide derivative which has PDE4 inhibiting activity, it is the following compound to the patent documents 5.

[Formula 6]



(Among a formula, R^3 is set to the low-grade alkenyl etc., R^4 sets H, low-grade alkyl, etc. to NR^3R^4, and R^1 and R^2 H, halogen, low-grade alkyl, and O-low-grade alkyl etc.) The nitrogen-containing heterocycle which is united with N which R^3 and R^4 combine, and may be replaced is shown. It is concerned referring to the gazette for details. It is the following compound to the patent documents 6.

[Formula 7]



(R^1 and R^2 show H, halogen, low-grade alkyl, and O-low-grade alkyl etc. among a formula, and R^5 shows H, low-grade alkyl, etc.) It is concerned referring to the gazette for details. Although indicated, respectively, the patent documents 5 and 6 are the literature exhibited by each after this application priority date.

[0009]

[Patent documents 1] The international publication 94th/No. 12461 pamphlet

[Patent documents 2] JP,56-7782,A

[Patent documents 3] The international publication 96th/No. 21645 pamphlet

[Patent documents 4] The international publication 96th/No. 21646 pamphlet

[Patent documents 5] JP,2003-64057,A

[Patent documents 6] The international publication 02nd/No. 102778 pamphlet

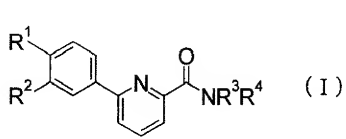
[Description of the Invention]

[Problem(s) to be Solved by the Invention]

[0010]

This invention persons could administer orally, checked PDE4 good and selectively, and inquired for the purpose of providing a useful medicinal composition and providing the medicine which contains these further for prevention and the therapy of respiratory illnesses, such as

bronchial asthma with few side effects, and COPD.
[Means for Solving the Problem]
[0011]
This invention persons took lessons from a compound which has inhibiting activity to PDE4, and inquired wholeheartedly. As a result, the knowledge of having PDE4 inhibitory action powerful [a new pyridine- 2-carboxamide derivative which has a phenyl group], and alternative was carried out to the 6th place, and this invention was completed.
[Effect of the Invention]
[0012]
Since the new pyridine- 2-carboxamide derivative which has a phenyl group in the 6th place shown by after-mentioned type (I) is excellent in the inhibiting activity of PDE4, the medicinal composition containing the compound concerned, It is useful as prevention and a treating agent of the respiratory illnesses (for example, bronchial asthma (atopic asthma is included), COPD, chronic bronchitis, a pneumonia nature disease, adult respiratory distress syndrome (ARDS), etc.) in which PDE4 participates. It is especially expectable as bronchial asthma, and prevention and the remedy of COPD. The disease of others by which the intervention of PDE4 is known as for the medicinal composition concerned, For example, the disease in which cytokine (IL-1, IL-4, IL-6, and TNF (tumor necrosis factor)) etc. participate. for example, articular rheumatism, ulcerative colitis, Crohn's disease, septicemia, and the septic shock. endotoxin shock, gram-negative-bacteria septicemia, toxic shock syndrome, a nephritis, hepatitis, infection (bacteria and virus), circulatory failure (cardiac insufficiency, arteriosclerosis, myocardial infarction, cerebral apoplexy), etc. -- etc. -- it is useful also as prevention and a remedy.
The crystal especially alpha type, and beta type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine of this invention are excellent in stability, and useful as a manufacture field object of the medicinal composition of this invention. beta type crystal fits the extensive composition in industrial production especially.
[Best Mode of Carrying Out the Invention]
[0013]
That is, this invention relates to the medicinal composition and the especially effective medicinal composition as prevention and remedies, such as bronchial asthma and COPD, which consist of the new pyridine derivative shown by following general formula (I) or its salt permitted pharmaceutically, and a carrier permitted pharmaceutically.
[0014]
[Formula 8]



(I)

(The sign in a formula shows a following meaning.)
R^1 and R^2 : Differ identically or mutually and H, halogen, Low-grade alkyl and O-low-grade alkyl, O- (low-grade alkyl replaced with halogen), NH_2, NH-low-grade alkyl, N(low-grade alkyl) $_2$, NHCO-low-grade alkyl, O-low-grade alkylene NH-low-grade alkyl, O-low-grade alkylene N(low-grade alkyl) $_2$, O-low-grade alkylene CO_2R^0, an O-low-grade alkylene hydrocarbon ring, O-low-grade alkylene heterocycle or R^1, and R^2 are united, and it is the -O-low-grade alkylene

O. -
R^0: H, low-grade alkyl, or CH_2 - (phenyl which may be replaced)
R^3 : A low-grade alkenyl, low-grade alkynyl, and hydrocarbon ring which may be replaced, Heterocycle which may be replaced, a hydrocarbon ring by which low-grade alkylene substitution may be carried out, Heterocycle, low-grade alkylene R^{51} by which low-grade alkylene substitution may be carried out, Low-grade alkylene CO_2R^0, low-grade alkylene $N(R^0)$-low-grade alkyl, $C(R^{53})$ (R^{54})-R^{55}, low-grade alkylene $C(R^{53})$ (R^{54})-R^{55}, or O-R^0,
R^4: H, low-grade alkyl, low-grade alkenyl, low-grade alkynyl, A hydrocarbon ring which may be replaced, heterocycle which may be replaced, A hydrocarbon ring by which low-grade alkylene substitution may be carried out, heterocycle by which low-grade alkylene substitution may be carried out, Low-grade alkylene R^{51}, low-grade alkylene CO_2R^0, Low-grade alkylene $N(R^0)$-low-grade alkyl, $C(R^{53})$ (R^{54})-R^{55}, or low-grade alkylene $C(R^{53})$ (R^{54})-R^{55},
R^{51}: CO-low-grade alkyl, CO- (hydrocarbon ring which may be replaced), CO- (heterocycle which may be replaced), and CO-low-grade alkylene (hydrocarbon ring which may be replaced), CO-low-grade alkylene (heterocycle which may be replaced), CN, OH, O-low-grade alkyl, O-(hydrocarbon ring which may be replaced), O- (heterocycle which may be replaced), and O-low-grade alkylene (hydrocarbon ring which may be replaced), O-low-grade alkylene (heterocycle which may be replaced), S-low-grade alkyl, S- (hydrocarbon ring which may be replaced), S-(heterocycle which may be replaced), S-low-grade alkylene (hydrocarbon ring which may be replaced), S-low-grade alkylene (heterocycle which may be replaced), NH (R^0), $N(CH_3)_2$, $N(C_2H_5)_2$, $N(R^0)$- (hydrocarbon ring which may be replaced), $N(R^0)$- (heterocycle which may be replaced), $N(R^0)$-low-grade alkylene (hydrocarbon ring which may be replaced), $N(R^0)$-low-grade alkylene (heterocycle which may be replaced). $N(R^0)$ CO-low-grade alkyl, $N(R^0)$ CO-(hydrocarbon ring which may be replaced), $N(R^0)$ CO- (heterocycle which may be replaced), and $N(R^0)$ CO-low-grade alkylene (hydrocarbon ring which may be replaced), $N(R^0)$ CO-low-grade alkylene (heterocycle which may be replaced), $N(R^0)$ CO-O-low-grade alkyl, $N(R^0)$ CO-O-low-grade alkylene (hydrocarbon ring which may be replaced), or $N(R^0)$ CO-O-low-grade alkylene (heterocycle which may be replaced),
R^{53}, R^{54}, and R^{55}: Differ identically or mutually and they are H, low-grade alkyl, and CO_2R^0, CON (R^0) (R^{56}), R^{51}, or R^{56},
R^{56}: A hydrocarbon ring which may be replaced, heterocycle which may be replaced, a hydrocarbon ring by which low-grade alkylene substitution may be carried out, heterocycle by which low-grade alkylene substitution may be carried out, low-grade alkylene R^{51}, or low-grade alkylene CO_2R^0,
Or nitrogen-containing heterocycle which is united with N which R^3 and R^4 combine, and may be replaced in NR^3R^4.
However, the following compounds are excluded. :
(1) When R^4 is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, phenyl, pyridyl, pyrimidyl, thiazolyl, or oxazolyl, R^3 C_{1-6} alkyl, (phenyl which may be replaced with C_{1-4} alkyl or halogen), $CH(R^{00})$ CO_2R^{00}, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, the C_{2-5} alkylene N (CH_3) (C_4H_9). Or a compound which is the C_{2-5} alkylene N (C_2H_5) (C_3H_7) (R^{00} differs identically or mutually and is H or C_{1-4} alkyl.),
When R^4 is H, R^3 (2) OH, C_{1-6} alkyl, (Phenyl which may be replaced with C_{1-4} alkyl or halogen), $CH(R^{00})$ CO_2R^{00}, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, the C_{2-5} alkylene N (CH_3) (C_4H_9). a compound which is the C_{2-5} alkylene N (C_2H_5) (C_3H_7), pyridyl, pyrimidyl, thiazolyl, oxazolyl, or tetra ZORIRU -- and
(3) Nitrogen-containing heterocycle formed in NR^3R^4 united with N which R^3 and R^4 combine, (i) 1 thru/or 2 C_{1-4} alkyls, CO_2R^{00}, $CONH_2$, $CON(CH_3)_2$, oxo, It may be replaced by OH, NH_2, or $N(CH_3)_2$, 1-pyrrolidyl or 1-piperidyl by which desaturation may be carried out; (ii).

Desaturation may be carried out. 4-morpholinyl or thio morpholine-4-yl; -- 1 by which the 4th place of (iii) may be replaced by methyl, acetyl, or benzyl, and desaturation may be carried out - a quinoline ring which may be replaced by PIPERAJIRU; or (iv) F -- coming out -- a certain compound. It is the same as that of the following.

In a compound shown by the above-mentioned general formula (I), especially 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine. It was desirable in (it may be hereafter written as "compound A"), and further, two sorts of crystal polymorphism existed in compound A, and it found out that any crystal was unexpectedly preferred as a manufacture field object of this invention medicinal composition. This invention also includes these crystals.

[0015]

Hereafter, this invention is explained in detail.

"Alkyl", "alkylene", "alkenyl", "alkenylene", "alkynyl", and "alkynylene" mean a hydrocarbon chain of straight chain shape or a letter of branching among this specification. "low-grade alkyl" is an alkyl group of 1-6 carbon numbers preferably -- more -- desirable -- an alkyl group of 1-4 carbon numbers -- they are methyl and ethyl still more preferably. "Low-grade alkylene" means a bivalence group from which one arbitrary hydrogen atom of the above "low-grade alkyl" is removed, is the alkylene of 1-4 carbon numbers preferably, and is methylene, ethylene, and propylene more preferably. "Low-grade alkenyl" means a basis which has one or more double bonds in arbitrary positions of with a carbon numbers of two or more "low-grade alkyl", and is alkenyl of 2-4 carbon numbers preferably. "Low-grade alkenylene" means a basis which has one or more double bonds in arbitrary positions of with a carbon numbers of two or more "low-grade alkylene", and is alkenylene of 2-4 carbon numbers preferably. "Low-grade alkynyl" means a basis which has one or more triple bonds in arbitrary positions of with a carbon numbers of two or more "low-grade alkyl", and is alkynyl of 2-4 carbon numbers preferably. "Low-grade alkynylene" means a basis which has one or more triple bonds in arbitrary positions of with a carbon numbers of two or more "low-grade alkylene", and is alkynylene of 2-4 carbon numbers preferably.

"Halogen" shows F, Cl, Br, and I. With "low-grade alkyl replaced with halogen." It is C_{1-6} alkyl which meant preferably alkyl of 1-6 carbon numbers replaced with one or more halogen, and was more preferably replaced by one or more F, and they are fluoromethyl, difluoromethyl, trifluoromethyl, and trifluoroethyl still more preferably.

[0016]

A "hydrocarbon ring" means 14 monocycles - a tricyclic hydrocarbon ring group from the carbon number 3, and contains cycloalkyl, cyclo alkenyl, aromatic hydrocarbon, cycloalkyl over which the bridge was constructed, and a spiro loop. They condense mutually and may form indanyl, tetrahydro naphthyl, etc.

"Cycloalkyl" is cycloalkyl of 3-8 carbon numbers preferably, and is cyclopropyl, cyclopentyl, and cyclohexyl more preferably. "Cyclo alkenyl" is cyclo alkenyl of 5-8 carbon numbers preferably, and is cyclohexenyl more preferably. "Aromatic hydrocarbon" means an aromatic hydrocarbon group of 6-14 carbon numbers, is phenyl and naphthyl preferably, and is phenyl more preferably. As "cycloalkyl over which the bridge was constructed", they are norbornyl and adamanthyl preferably.

[0017]

the monocycle 3 of saturation containing 1 thru/or 4 hetero atoms in which "heterocycle" is chosen from O, S, and N as a ring atom, or an unsaturation - 8 members -- it is 5 - 7 member heterocycle preferably, and it may condense the ring with the heterocycles concerned or a cycloalkyl ring, and the benzene ring, and tricyclic heterocycle may be formed from 2. S or N which is a ring atom may oxidize, and oxide and dioxide may be formed. Arbitrary carbon atoms

may be replaced [in / including saturation heterocycle, aromatic heterocycle, and its heterocycle saturated selectively / in the heterocycle concerned / saturation heterocycle and heterocycle saturated selectively] by an oxo group. The bridge may be constructed over the heterocycle concerned and it may form a spiro loop (acetal objects, such as a 1,3-dioxolane ring derived from an oxo group, are included). This heterocycle is 5 thru/or 7 member saturation or an unsaturation monocycle heterocycle group preferably, and are pyrrolidine, pyridine, piperidine, morpholine, a thiophene, a thiazole, imidazole, tetrazole, pyrazine, and a piperazine more preferably. "nitrogen-containing heterocycle" shows a heterocycle group which has one or more N atoms as a ring atom in the above "heterocycle", and is 5 thru/or 7 member saturated monocyclic heterocycle group preferably -- more -- desirable -- pyrrolidine, piperidine, morpholine, and a piperazine -- it is a piperazine still more preferably.

[0018]

"No replacing" or "having 1-5 same or different substituents" are shown ["it may be replaced" and].

A substituent in "nitrogen-containing heterocycle which may be replaced", Preferably Low-grade alkyl, halogen, OH, NH_2, $N(R^0)$-low-grade alkyl, CO_2R^0, $CONH_2$, $CON(R^0)$-low-grade alkyl, A hydrocarbon ring which may be replaced, heterocycle which may be replaced, A hydrocarbon ring by which low-grade alkylene substitution may be carried out, heterocycle by which low-grade alkylene substitution may be carried out, A hydrocarbon ring by which low-grade alkenylene substitution may be carried out, heterocycle by which low-grade alkenylene substitution may be carried out, Low-grade alkylene R^{51}, low-grade alkylene CO_2R^0, CO-low-grade alkyl, CO- (hydrocarbon ring which may be replaced), CO- (heterocycle which may be replaced), and CO-low-grade alkylene (hydrocarbon ring which may be replaced), CO-low-grade alkylene (heterocycle which may be replaced), CN, O-low-grade alkyl, O- (hydrocarbon ring which may be replaced), O- (heterocycle which may be replaced), and O-low-grade alkylene (hydrocarbon ring which may be replaced), O-low-grade alkylene (heterocycle which may be replaced), S-low-grade alkyl, S- (hydrocarbon ring which may be replaced), S- (heterocycle which may be replaced), S-low-grade alkylene (hydrocarbon ring which may be replaced), S-low-grade alkylene (heterocycle which may be replaced), $N(R^0)$- (hydrocarbon ring which may be replaced), $N(R^0)$- (heterocycle which may be replaced), $N(R^0)$-low-grade alkylene (hydrocarbon ring which may be replaced), $N(R^0)$-low-grade alkylene (heterocycle which may be replaced), $N(R^0)$ CO-low-grade alkyl, $N(R^0)$ CO- (hydrocarbon ring which may be replaced), $N(R^0)$ CO- (heterocycle which may be replaced), $N(R^0)$ CO-low-grade alkylene (hydrocarbon ring which may be replaced), $N(R^0)$ CO-low-grade alkylene (heterocycle which may be replaced), $N(R^0)$ CO-O-low-grade alkyl, $N(R^0)$ CO-O-low-grade alkylene (hydrocarbon ring which may be replaced), $N(R^0)$ CO-O-low-grade alkylene (heterocycle which may be replaced), CO-O-low-grade alkylene (hydrocarbon ring which may be replaced), CO-O-low-grade alkylene (heterocycle which may be replaced), CON (R^0) (R^{56}), $C(R^{53})$ (R^{54})-R^{55}, or low-grade alkylene $C(R^{53})$ (R^{54})-R^{55} -- it comes out.

[0019]

A substituent in "a hydrocarbon ring which may be replaced", or "heterocycle which may be replaced" is a basis shown in following G group preferably.

G group: A basis shown by the (i) -X-C_{1-6} alkylene A, the (ii) -C_{1-6} alkylene A, or (iii) -B.

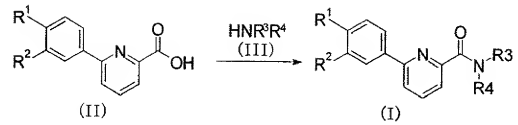
It is here,

X O, S, SO, SO_2, NH, N (C_{1-6} alkyl), SO_2NH, SO_2N (C_{1-6} alkyl), $NHSO_2$, $N(C_{1-6}$ alkyl) SO_2, CO, CO_2, O-CO, CONH, CON (C_{1-6} alkyl), NHCO, $N(C_{1-6}$ alkyl) CO, or NHCONH,

A -CN, -OH, -CO_2H, -CO_2-C_{1-6} alkyl, - NO_2, -SO_3H, -NH_2, -$CONH_2$, - SO_2NH_2, C_{1-6} alkyl replaced with halogen, - NH-C_{1-6} alkylene O-C_{1-6} alkyl, -N(C_{1-6} alkyl)-C_{1-6} alkylene O-C_{1-6} alkyl, -N (-C_{1-6} alkylene O-C_{1-6} alkyl) $_2$, - A hydrocarbon ring, - heterocycle, -X-C_{1-6} alkyl, C_{1-6} alkyl

replaced with -X-halogen, -X-hydrocarbon ring, -X-heterocycle, the -X-C_{1-6} alkylene CN, -The X-C_{1-6} alkylene OH, -X-C_{1-6} alkylene CO_2H, -X-C_{1-6} alkylene CO_2-C_{1-6} alkyl, -X-C_{1-6} alkylene NO_2, and -X-C_{1-6} alkylene SO_3H, -X-C_{1-6} alkylene NH_2, -X-C_{1-6} alkylene $CONH_2$, -X-C_{1-6} alkylene SO_2NH_2, a -X-C_{1-6} alkylene hydrocarbon ring, or -X-C_{1-6} alkylene heterocycle,
B is C_{1-6} alkyl replaced with -C_{1-6} alkyl, - halogen, and halogen, or a basis given in A,
A hydrocarbon ring and heterocycle in the above A and B, C_{1-6} alkyl replaced with C_{1-6} alkyl, halogen, and halogen, CN, OH, O-C_{1-6} alkyl, NH_2, NH-C_{1-6} alkyl, $N(C_{1-6}$ alkyl$)_2$, S-C_{1-6} alkyl, SO-C_{1-6} alkyl, SO_2-C_{1-6} alkyl, SO_2NH_2, SO_2NH-C_{1-6} alkyl, $SO_2N(C_{1-6}$ alkyl$)_2$, $NHSO_2$-C_{1-6} alkyl, It may have from 1 five substituents chosen from CO_2H, CO_2-C_{1-6} alkyl, $CONH_2$, CONH-C_{1-6} alkyl, $CON(C_{1-6}$ alkyl$)_2$, and NHCO-C_{1-6} alkyl.
[0020]
A substituent in "phenyl which may be replaced" is a basis shown in the above-mentioned G group preferably, and is C_{1-6} alkyl, O-C_{1-6} alkyl, or halogen still more preferably.
[0021]
A desirable compound in general formula (I) of this invention is the following compound or its salt permitted pharmaceutically. :
R^1 -- O-C_{1-6} alkyl -- more -- desirable -- O-C_{1-4} alkyl and a compound which is O-methyl still more preferably. R^2 -- halogen, O-C_{1-6} alkyl, or an O-C_{1-6} alkylene hydrocarbon ring -- more -- desirable -- halogen, O-C_{1-4} alkyl or O-CH_2-C_{3-8} cycloalkyl, and a compound that is O-methyl still more preferably. NR^3R^4 is a compound of NH-$CH(R^{53})$-R^{55} or N (hydrocarbon ring) (heterocycle by which C_{1-6} alkylene substitution may be carried out), Heterocycle which a hydrocarbon ring, especially phenyl are preferred here as R^{53}, and may be replaced by it as R^{55}, especially a pyridyl group which may be replaced are preferred. As a mode of another desirable NR^3R^4, it is piperazine 1-yl, The 4th place of the piperazine 1-yl concerned is the compound replaced by a hydrocarbon ring which may be replaced, or heterocycle which may be replaced, a basis by which the 4th place of the piperazine 1-yl concerned is the compound replaced by phenyl which may be replaced, or pyridyl which may be replaced, and the phenyl concerned and pyridyl are more preferably chosen from said G group here -- desirable -- 1 -- or it has two pieces one piece more preferably.
[0022]
Also in general formula (I) of this invention, a desirable compound is the following compound or its salt permitted pharmaceutically. :
A 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-(4-methoxypheny) piperazine, N-[(1-benzyl piperidine- 4-yl) (phenyl) methyl]-6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide, 6-(3,4-dimethoxyphenyl)-N-[phenyl(pyridin-4-yl) methyl] pyridine- 2-carboxamide, N-(1-benzyl-4-phenyl-4-piperidyl)-6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide, 6-(3,4-dimethoxyphenyl)-N-(2-morpholino 1-phenoxy methylethyl) pyridine- 2-carboxamide, 6-(3,4-dimethoxyphenyl)-N-(2-morpholino ethyl)-N-(1,2,3,4-tetrahydro 1-naphthyl) pyridine- 2-carboxamide, trans-6-(3,4-dimethoxyphenyl)-N-(2-methoxy ethyl)-N-(2-methylsulfanyl cyclopentyl) pyridine- 2-carboxamide, 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-N,N-diethyldecahydronaliumquinolin-2-carboxamide, 1-(4-{4-[6-(3-cyclopropylmethoxy-4-methoxypheny) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) ethanone, 4'-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} acetanilide, A 3-diethylamino 4'-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} propane anilide, 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine, A 1-[2-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) ethyl] piperidine- 4-oar, 4-{2-[(6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl}-3-pyridyl) oxy] ethyl} morpholine, trans-5-. (4-{4-[6-.) 3. 4-dimethoxyphenylpyridine- 2-carbonyl]-2, 5-dimethylpiperazine 1-yl} phenylpentanoic acid and 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-

carbonyl]-4-{4-[(1-oxide 4-pyridyl) methoxy] phenyl} piperazine. In particular, 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine is preferred.
[0023]
A thing from which these isomers separated into this invention compound (I) which is an active principle of this invention although geometric isomer and a tautomer may exist depending on a kind of substituent, or a mixture is included.
Compound (I) may have an asymmetric carbon atom and an optical isomer of the (R) object based on this and the (S) object may exist. This invention includes all of a mixture and a thing which isolated of these optical isomers.
A prodrug permitted pharmacologically is also contained in compound (I). A prodrug permitted pharmacologically is a compound which has a basis convertible into NH_2 of this invention, OH, CO_2H, etc. solvolysis or under physiological conditions. as the basis which forms a prodrug -- Prog. Med., 5, 2157-2161 (1985), and the 7th volume of "development of drugs" (Hirokawa Publishing, 1990) A basis of a statement is mentioned to the molecular design 163-198.
[0024]
Compound (I) may form a salt with a base depending on a kind of acid addition salt or substituent. As this salt, are a salt permitted pharmaceutically, and specifically, Inorganic acid, such as chloride, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, and phosphoric acid, Formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, Maleate, lactic acid, malic acid, tartaric acid, citrate, methanesulfonic acid, Acid addition salt with organic acid, such as ethane sulfonic acid, aspartic acid, and glutamic acid, Salts, ammonium salt, etc. with an organic base, such as inorganic bases, such as sodium, potassium, magnesium, calcium, and aluminum, methylamine, ethylamine, ethanolamine, lysine, and ornithine, are mentioned.
This invention also includes a medicinal composition containing a substance of compound (I), various kinds of hydrates of the salt and solvate, and crystal polymorphism.
[0025]
(Manufacturing method)
Compound (I) which is an active principle of this invention, and its salt permitted pharmaceutically can use the basic skeleton or the feature based on a kind of substituent, and can manufacture it with the application of various publicly known synthetic methods. In that case, it may be effective on production technology to transpose the functional group concerned to a basis which can be converted easily by a suitable protective group in a stage of a raw material thru/or an intermediate at protection or the functional group concerned depending on a kind of functional group. As such a functional group, they are an amino group, a hydroxyl group, a carboxyl group, etc., As those protective groups, for example, green (T. W. Greene) and Wuts (P. G. M. Wuts) work, What is necessary is to be able to mention a protective group of a statement to "Protective Groups in Organic Synthesis (the 3rd edition, 1999)", to choose these suitably according to a reaction condition, and just to use them. In such a method, after reacting by introducing the protective group concerned, a desired compound can be obtained by converting a protective group into a basis of removal or a request if needed.
A prodrug of compound (I) can be manufactured like the above-mentioned protective group at reacting a specific basis using introduction or obtained compound (I) in a stage of a raw material thru/or an intermediate. The reaction can perform the usual esterification, amidation, drying, etc. by applying a publicly known method by a person skilled in the art.
[0026]
The 1st process
[Formula 9]



(II) (I)

This process is a method of manufacturing compound (I) by an amidation reaction from carboxylic acid compound (II).

[0027]

a reaction -- compound (II) -- a condensing agent (for example, dicyclohexylcarbodiimide (DCC).) A diisopropylcarbodiimide (DIPC), a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (WSC), Depending on the case, 1,1'-carbonyl bis-1H-imidazole (CDI) etc. It can carry out by condensing with amine compound (III) under existence of additive agents (for example, N-hydroxysuccinimide (HONSu), 1-hydroxybenzotriazol (HOBt), etc.). The active ester object of compound (II) and the above-mentioned additive agent may once be condensed with amine compound (III) after isolation. As a solvent, for example Aromatic hydrocarbon, such as benzene, toluene, and xylene. Diethylether, a tetrahydrofuran (THF), 1,4-dioxane, Halogenated hydrocarbon, such as ether, such as dimethoxyethane, dichloromethane, 1,2-dichloroethane, and chloroform, N.N-dimethylformamide (DMF), N-methyl-2-pyrrolidone (NMP), pyridine, etc. are mentioned. These solvents are independent, or two or more sorts are mixed and they are used.

[0028]

The 2nd process

A compound which has various substituents on basis R^3 in general formula (I) or R^4, R^1, or R^2 a compound which is a basis besides alkoxy Motomochi, It is easily compoundable by using obvious reactions or these strange methods for a person skilled in the art by using compound (I) as a raw material. For example, the following reactions are applicable.

(1) Alkylation by nucleophilic substitution

O-, S-, or N-alkylation reaction can be manufactured by making a compound which has OH, SH or the first class thru/or the third class amino group, and alkylating agents, such as alkyl halide, such as alkyl chloride, or organic-sulfonic-acid ester, react. Or it can manufacture also by giving the Mitsunobu reaction. It is carried out under cooling - heating using an excessive quantity of equivalents or one side among an organic solvent [inertness / reactions /, such as aromatic hydrocarbon, ether, alcohols (methanol, ethanol, etc.), DMF, NMP, and dimethyl sulfoxide (DMSO),]. Sodium hydride, potassium hydride, lithium diisopropylamide, When making it react under existence of bases, such as lithium hexamethyl JISHIRAJIDO, sodium methoxide, potassium tert-butoxide, sodium hydroxide, a potassium hydrate, sodium carbonate, and potassium carbonate, advances a reaction smoothly, it may be advantageous.

(2) Reductive alkylation

It can alkylate by making a compound which has the first class or the second class amine, and carbonyl compounds, such as ketone and aldehyde, react. The reaction can use a conventional method of reductive alkylation (if it sees from a carbonyl compound reductive amination), for example, a method of a statement is mentioned to 20 Chemical Society of Japan editing "experimental science lecture (4th edition)" (1992) (Maruzen) etc.

[0029]

(3) Amidation, sulfonamide-izing, and esterification

It can manufacture using carboxylic acid or a sulfonic acid compound by a method of using

methods of using a condensing agent of said 1st process, or those reactive derivatives. As a reactive derivative of carboxylic acid or a sulfonic acid compound, acid halide, an acid anhydride, active ester, etc. can be used. A reaction can be performed to 22 Chemical Society of Japan editing "experimental science lecture (4th edition)" (1992) (Maruzen) etc., for example by a method of a statement.

(4) Hydrolysis

By hydrolyzing a carboxylate object, this invention compound which has a carboxyl group can be manufactured. The reaction can use a conventional method of hydrolysis, for example, can apply a method of a statement to a deprotection reaction of a carboxyl group of the above-mentioned "Protective Groups in Organic Synthesis (the 3rd edition)", etc.

[0030]

(5) Oxidation

Oxide compounds, such as pyridine N-oxide, can be manufactured by oxidizing a compound which has pyridine, an amino group, etc. As an oxidizer, organic oxidants, such as inorganic oxidants, such as hydrogen peroxide, Oxone (a trade name, Aldrich), and sodium perborate, peracetic acid, m-chloroperbenzoic acid, and dimethyl dioxirane, can be used. A reaction is performed in a solvent [inertness / reactions /, such as halogenated hydrocarbon, aromatic hydrocarbon, ether, DMF, acetic acid, and water,] and under a non-solvent, cooling - heating. When reacting, an oxidizer can be used for the equivalent or an excess to a raw material compound, and it is inorganic acid (preferably). When making it react under existence of sulfuric acid, nitric acid, chloride, hydrobromic acid, organic acid (preferably acetic acid, trifluoroacetic acid), and an inorganic base (preferably sodium hydroxide, a potassium hydrate, sodium bicarbonate) advances a reaction smoothly, it may be advantageous. Sulfinyl or a sulfonyl compound can be manufactured by giving the same oxidation reaction using a sulfanil compound.

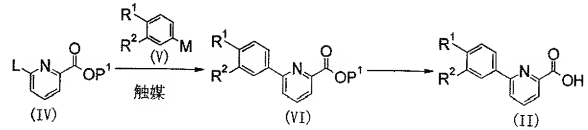
(6) Catalytic reduction

this invention compound which has an OH radical can be manufactured by giving a compound which has O-benzyl to a debenzylation reaction. For example, a conventional method of catalytic reduction which reacts under existence of a palladium carbon catalyst can be used under a hydrogen atmosphere, and a method of a statement can also be applied to a deprotection reaction of an OH radical of the above-mentioned "Protective Groups in Organic Synthesis (the 3rd edition)", etc. An alkenyl group is convertible for an alkyl group by a method of same catalytic reduction.

[0031]

Raw material composition

[Formula 10]



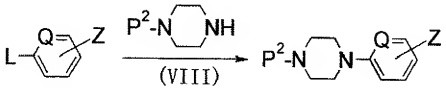
(L shows a leaving group among a formula, P^1 shows the protective group of a carboxyl group, and M shows metal, respectively.) It is the same as that of the following.

Carboxylic acid compound (II) can be manufactured by hydrolyzing compound (VI). Protective group P^1 can apply the protective group of the carboxyl group of the above-mentioned

"Protective Groups in Organic Synthesis (the 3rd edition)", and can remove it with the deprotection reaction of a statement, the conventional method of hydrolysis, etc. in the literature. Raw material compound (VI) can be manufactured by carrying out coupling of pyridine derivative (IV) and aryl metallic-compounds (V) under catalyst existence. The reaction can apply the method of a statement to Comprehensive Organic Synthesis, Volume 3, 481, and 1991 grades. Halogen, trifluoromethane sulfonyloxy, etc. are mentioned as the leaving group L, and hydroxyboron, alkyl boron, alkoxy boron, magnesium halide, zinc halide, ARUKIRUZUZU, alkyl copper, etc. are mentioned as the metal M, for example. As a catalyst, nickel complexes, such as palladium complexes, such as tetrakistriphenyl phosphinepalladium and palladium acetate, or dichlorobis (triphenyl phosphine) nickel, and bis(1,5-cyclo-octadiene)nickel, are preferred. A reaction is performed in a solvent [inertness / reactions /, such as halogenated hydrocarbon, ether, aromatic hydrocarbon, DMF, and water,] and under a non-solvent, cooling - heating. When reacting, the equivalent or one side can be superfluously used for compound (IV) and aryl metallic-compounds (V), When making it react under existence of bases, such as triethylamine, pyridine, 4-(N,N-dimethylamino) pyridine, sodium hydroxide, sodium carbonate, sodium hydride, methoxy sodium, or tert-butoxypotassium, advances a reaction smoothly, it may be advantageous.

[0032]

[Formula 11]



(VII) (IX)

(As for Q, P^2 shows among a formula the basis etc. as which Z is chosen [N / CH or] from G group in the protective group of H or an amino group, respectively.)

Raw material compound (IX) is compoundable by giving aryl derivative (VII) to a coupling reaction or an ipso substitution reaction with the piperazine which may be protected. The coupling reaction can apply the method of a statement to the manufacturing method of said raw material compound (VI). The ipso substitution reaction can apply the conditions of alkylation by the aforementioned (1) nucleophilic substitution. Protective group P^2 can apply the protective group of the amino group of the above-mentioned "Protective Groups in Organic Synthesis (the 3rd edition)", and can remove raw material compound (IX) by the deprotection reaction of a statement in the literature after a reaction.

[0033]

The resultant acquired by each above-mentioned process isolates as various kinds of solvates, such as an isolation compound, its salt, or a hydrate, and is refined. A salt can be manufactured by giving the usual salt formation processing.

Isolation and refining are performed with the application of the usual chemical operation, such as extraction, concentration, distilling off, crystallization, filtration, recrystallization, and various chromatography.

Various isomers can isolate with a conventional method using a physicochemical difference between isomers. For example, an optical isomer is separable with a general optical-resolution method, for example, fractional-crystallization-izing, or chromatography. An optical isomer can also be manufactured from a suitable optical activity raw material compound.

[0034]
This invention relates also to a crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine (compound A). The crystal of this invention should just be a crystal stable to a grade usable as a medicinal manufacture field object, and alpha type which has especially the following property value, or a beta type crystal is preferred. Each crystal is characterized by the following powder X diffraction spectrum [2 theta (degree)], respectively. In identity authorization of a crystal, a crystalline-lattice interval and an overall pattern are important for a powder X diffraction on character of data, and since it may change somewhat according to the direction of crystal growth, a size of particles, and a measuring condition, relative intensity should not be understood strictly.
alpha type: 10.82, 12.86, 16.96, 19.90, 21.76 and 22.88.
beta type: 11.66, 14.92, 16.92, 19.44, 20.10, 21.06 and 21.90.
As for beta type crystal, alpha type crystal has a heat-absorptive peak (extrapolation starting temperature (onset)) at 126-130 ** by DSC analysis at 138-142 **, respectively.
[0035]
Under 75% of 40 ** relative humidity, or 80 **, for two months, it is stable, and is usable as a medicinal manufacture field object, and alpha type and any beta type crystal are especially preferred as an original object of solid preparations. It is easy to crystallize alpha type crystal by performing recrystallization from ethyl acetate, and a crystal mixture of alpha type crystal and beta type crystal may be produced on the conditions. alpha type crystal can be obtained with sufficient reproducibility by using a seed crystal of alpha type crystal and performing recrystallization from an ethyl acetateethanol mixed solvent. On the other hand, beta type crystals are solvents, such as ethyl acetate, methanol, ethanol, and acetone, or those mixed solvents (preferably) about a crystal mixture of alpha type crystal and beta type crystal. It can obtain by making ethyl acetateethanol, acetoneethanol, or acetone methanol suspended, and stirring. beta type crystal can be obtained with sufficient reproducibility by using a seed crystal of beta type crystal and performing recrystallization from the above-mentioned mixed solvent. Since beta type crystal is convertible for beta type crystal by agitation treatment under suspension even if it being easy to deposit even if it changes a kind of solvent, and alpha type crystal are intermingled, it is suitable also for manufacture with a large scale in industrial production. This invention also includes a mixture containing alpha type crystal, beta type crystal, and them.
[0036]
Pharmaceutical preparation which contains one sort of compound (I) or its salt or two sorts or more as an active principle is prepared using a carrier, and an excipient and other additive agents which are usually used for pharmaceutical preparation-ization.
Administration may be which gestalt of parenteral administration by injections, such as internal use by tablet, pill, capsule, granule, powder medicine, liquids and solutions, etc. or intravenous injection, and intramuscular injection, suppositories, an endermic agent, a pernasal agent, inhalations, etc. Although suitably determined according to each case in consideration of condition, age for administration, sex, etc., when it is internal use, doses are adult 1 sunny 0.001 mg/kg thru/or a 100 mg/kg grade, and are 1 time about this, or are usually prescribed for the patient in 2 to 4 steps. a case where vein administration is carried out by condition -- usually -- per adult -- the range of 0.0001 mg/kg thru/or 10 mg/kg -- one day -- 1 time -- or a multiple dose is carried out. a case of inhalation -- usually -- per adult -- the range of 0.0001 mg/kg thru/or 1 mg/kg -- one day -- 1 time -- or a multiple dose is carried out.
A tablet, powder medicine, a granule, etc. are used as a solid constituent for internal use by this invention. In such a solid constituent, one or an active substance beyond it, It is mixed with at least one inertness excipient, for example, milk sugar, mannitol, grape sugar,

hydroxypropylcellulose, microcrystalline cellulose, starch, a polyvinyl pyrrolidone, magnesium aluminometasilicate, etc. A constituent may contain disintegrator, such as lubricant, such as an inertness additive agent, for example, magnesium stearate etc., and carboxy-methyl-starch sodium, and a solubilizing agent in accordance with a conventional method. The tunic of a tablet or the pill may be carried out by glycocalyx, stomach solubility, or an enteric coating agent as occasion demands.

[0037]

A liquid composition for internal use contains an inertness solvent generally used, for example, purified water, and ethanol including an emulsion, liquids and solutions, suspension, syrups, elixirs, etc. which are permitted in drugs. This constituent may contain a solubilizing agent, a wetting agent, an adjuvant like a suspending agent, a sweetening agent, corrigent, an aromatic, and an antiseptic in addition to an inertness solvent.

As injections for parenteral administration, sterile water or non-aqueous liquids and solutions, suspension, and an emulsion are included. As a water solvent, distilled water for injection and a physiological saline are contained, for example. As a non-aqueous solvent, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (trade name), etc., for example. Such a constituent may also contain an isotonizing agent, an antiseptic, a wetting agent, an emulsifier, a dispersing agent, a stabilizing agent, and a solubilizing agent further. These are sanitized by combination or an exposure of filtration and a germicide which lets for example, a bacteria suspension filter pass. These manufacture a sterile solid constituent, and they can also use it for aseptic water or a sterile solvent for injection before use, dissolving and suspending them to it.

Inhalations, a pernasal agent, etc. pass, a thing of a solid, a fluid, and the shape of a semisolid is used, and a membrane agent can be conventionally manufactured in accordance with a publicly known method. For example, lactose, an excipient like starch and also a pH adjuster and an antiseptic, a surface-active agent, lubricant, stabilizer, a thickener, etc. may be added suitably. The administration can use a device for suitable inhalation or insufflatio. For example, publicly known devices and spray pumps, such as a measuring administration inhalation device, can be used, and a medicine can be prescribed for the patient as a solution or suspension combining a carrier which can permit a compound in medicine as powder of independent or a prescribed mixture. Inhalers may be [a single time or] for many administration, and an end of dried powder or powder content capsule can be used for them in the end of dried powder. Or it may be a gestalt of an application-of-pressure aerosol spray etc. which use suitable gases, such as a suitable ejection agent, for example, chlorofluoroalkane, hydronaliumfluoroalkane, or carbon dioxide.

[0038]

A medicinal composition which contains a pyridine derivative of this invention, or its salt permitted pharmaceutically as an active principle, It may use together, combining suitably beta2 agonists, such as other remedially effective active principles, for example, formoterol etc., a steroid, an anticholinergic drug agent, a leukotriene antagonist, lipoxygenase inhibitor, cytokine inhibitor, etc. When using together with these, in order to prescribe a medicine for the patient one by one, it may be used as separate pharmaceutical preparation put together as a combination drug for prescribing a medicine for the patient simultaneously.

[Example]

[0039]

Hereafter, although an example explains this invention concretely, these do not limit the range of this invention. The process of the phenylpyridine derivative which is a medicinal active principle of this invention is shown in the example of manufacture, and the process of the raw material compound of the compound concerned is shown in a reference example.

Example 1 (PDE4 inhibiting activity)
1) The solution containing PDE4 was refined from the rat ventricle muscle as follows. The physiological saline separated the ventricle for the heart extracted under anesthesia from male Wistar rats after washing. the buffer solution A (20 --) which comes out on both sides of the separated ventricle, cuts finely, and contains PROTEASE INHIBITOR COCKTAIL For Mammalian Cell Extracts (SIGMA) for this 1% [mM Bis-Tris and] 50 mM sodium acetate, 2 mM EDTA, and 5 mM 2-mercaptoethanol, 2 The cell was destroyed by polyTRON after being suspended to mM benzamidene, 0.05 mM phenyl-methyl-sulfonyl-fluoride, and pH 6.5, and the soluble fraction was obtained by carrying out ultracentrifuge (for 100,000 G and 60 minutes, 4 **).
2) The 2.6x10 cm Q sepharose column equilibrated with the buffer solution A was filled up with the obtained soluble fraction. Subsequently, this column was washed by buffer solution A 1200 ml, and uncombined protein was removed. The protein combined with this column was eluted using buffer solution A 750 ml containing the linearity inclination liquid of 0.05 - 1.00 M sodium acetate, and 110 7 ml fractionation was collected. It inspected about the cAMP metabolic turnover PDE activity of each fractionation obtained under cGMP and calcium / calmodulin existence, or nonexistence. The fractionation which has the metabolic activity of cAMP in each fractionation and in which cAMP metabolic activity does not receive influence by existence of cGMP, or calcium/calmodulin was used as a stock solution for inspecting PDE4 inhibiting activity.
A test compound the concentration of a request 3) 40 mM Tris-HCl (pH 8.0), 5 mM magnesium chloride, 4 mM 2-mercaptoethanol, 1microM cAMP, and 1 muCi/ml It was made to react for 10 minutes at 30 ** in the reaction mixed liquor which [^{3}H] cAMP and PDE4 stock solution contains. 18 mM sulfate of zinc of a moiety [reaction mixture], 5 Add the 20 mg/ml Polylysine coated yttrium silicate SPA beads (Amersham) suspension containing muM 3-ISOBUTYL-1-METHYLXANTHINE (IBMX), and stop a reaction, Radioactivity was measured.
IC_{50} considered it as the test compound concentration which checks the metabolic activity of PDE4 50%, and computed about each compound.
The above-mentioned examining method and the method given in WO97/19078 gazette were applied, and PDE1, PDE2, PDE3, and PDE5 inhibiting activity was measured similarly.
Compound (I) shows good inhibiting activity to PDE4 as a result of the above-mentioned measurement, The compound of the examples 2, 4, 5, 36, 48, 57, 75, 82, 96, 99, 137, 164, 171, 180, 191, 199, and 210 of the after-mentioned manufacture showed the powerful activity below of 12 nM in IC_{50} especially. The concentration hardly showed inhibiting activity to PDE1, PDE2, PDE3, and PDE5. Therefore, it was checked that it is PDE4 inhibitor whose compound (I) was alternative and which was excellent.
[0040]
Example 2 (oral absorbency evaluation test which made TNF-alpha production inhibiting activity the index)
1) Test compound 10 mg/kg suspended to methyl cellulose purified water 0.5% was administered orally to the 8-weeks old male Fischer rat. The control group was similarly medicated with the solvent (0.5% methyl cellulose purified water, 3 ml/kg). After internal use, from the caudal vein of the rat which performed anesthesia temporally, it collected blood under heparin existence and plasma was prepared in accordance with the conventional method.
2) So that the whole quantity per hole may be set to 200microl at 96 hole culture plate, Whole blood 20mul of the plasma (2.5% of the last concentration) prepared in the top, RPMI1640 culture medium which contains fetal calf serum 10%, and male Wistar rats, and LPS (the 3 microg/ml last concentration) were poured distributively, and it cultivated at 37 ** overnight using CO_2 incubator. Centrifugality (for 1500 r.p.m. and 10 minutes) of the plate was carried out

after the end of culture, supernatant liquid was collected, and the amount of TNF-alpha in supernatant liquid was measured using commercial ELISA kit.
It became clear that the example compound of manufacture had good oral absorbency as a result of the above-mentioned examination.
It is clear that compound (I)'s it is useful as the prevention and a remedy of a disease in which it is checked as a result of the above-mentioned inhibiting activity measurement test that alternative and powerful inhibiting activity is shown to PDE4, and PDE4 involves since oral absorbency is also good.
[0041]
Example 3 (operation on the eosinophil leukocytic infiltrate in an antigen induction rat respiratory tract)
Antigen sensitization was performed to a 4-weeks old Brown Norway system feminity rat (Japanese CHARU sliver, Kanagawa) by continuing for three days and carrying out 1 ml intraperitoneal injection of the OA solution for sensitization (the last concentration: OA;1 mg/ml, aluminum(OH) $_3$;20 mg/ml) per animal. The administration first day was set to Day 0. 1%OA / physiological salt solution was atomized with the ultrasonic nebulizer (NE-U12, OMRON) to Day 21 or 22, antigen exposure was carried out by making a sensitization rat inhale for 20 minutes, and permeation of the eosinophile leucocyte into a respiratory tract was caused. The group which carried out inhalation exposure of the physiological salt solution was used as a normal control group. It was suspended in MC solution 0.5%, and the test compound was administered orally 1 hour before the antigen inhalation exposure start. From the day preceding antigen inhalation exposure, the animal was considered as the fast and canceled the fast after antigen inhalation exposure. After making an incision in the abdomen under the Nembutal anesthesia and carrying out bleeding fatality of the animal from an abdominal aorta 24 hours after antigen inhalation exposure, By inserting cannula (6 Fr-atom catheterization of vein, atom) in a trachea, and repeating operation of pouring in and collecting the heparin (1 unit/ml) content physiological salt solutions of 2 ml, 5 times (a total of ten ml(s)), Broncho-alveolar lavage (BAL:Bronchoalveolar Lavage) was performed. Supernatant liquid was removed for the collected BAL liquid after centrifugality by 500xg (for 4 ** and 10 minutes), and the dregs (cell fraction) were re-suspended with a heparin (1 unit/ml) content physiological salt solution of 500microl. After measuring the total leukocyte concentration of re-suspension with blood cell counters (Celltac-alpha, Nihon Kohden), the smear was produced, it observed under the microscope after dyeing with the blood stain solution for differentiation (DIFU quick, International Reagents), and the rate of an abundance ratio of eosinophile leucocyte was computed from the morphological feature. From the total white blood cell count and the rate of an eosinophile leucocyte abundance ratio, the total of the number of eosinophile leucocytes was computed and the effect of the drug was evaluated.
The compound of the examples 2, 36, and 180 of manufacture showed 60%, 92%, and 31% of inhibiting activity in internal use of 3.0 mg/kg, respectively as a result of the above-mentioned measurement. Although the compound (compound A) of the example 36 of manufacture used alpha type crystal in the exam, since alpha type crystal and beta type crystal have almost equivalent solubility to water and pH 1.2 or pH 6.8 buffer solution, beta type crystal is considered to be effective the same way.
[0042]
Example 4 (operation on the neutrophilic infiltration in a rat LPS induction respiratory tract)
the 6-weeks old Wistar system male rat (Japanese CHARU sliver.) which anesthetized by injecting intraperitoneally optimum dose of ketamine / KISHIRAJIN mixed liquor 10 microg [which was dissolved in a physiological salt solution in Kanagawa]/ml LPS Permeation of the neutrophil leucocyte into a respiratory tract was caused by prescribing a solution

(Lipopolysaccharide E.coli 0127:B8 Boivin, DIFCO) for the patient in a respiratory tract using a 200microl sound. The group which prescribed a physiological salt solution for the patient in the respiratory tract was used as a normal control group. It was suspended in MC solution 0.5%, and the test compound was administered orally 1 hour before the administration in an LPS respiratory tract. From the day preceding the administration in an LPS respiratory tract, the animal was considered as the fast and canceled the fast after the administration in an LPS respiratory tract. 24 hours after the administration in an LPS respiratory tract, after making an incision in the abdomen under the Nembutal anesthesia and carrying out bleeding fatality of the animal from an abdominal aorta, the total leukocyte concentration was measured like the following above-mentioned example 3. The rate of an abundance ratio of neutrophil leucocyte was similarly computed from the morphological feature observed under the microscope. From the total white blood cell count and the rate of a neutrophil leucocyte abundance ratio, the total of the number of neutrophil leucocytes was computed and the effect of the drug was evaluated.

[0043]

The cable address below the inside of a reference example and the after-mentioned table is used. the example number of Ex:manufacture, and Dat:physicochemical data (F:FAB-MS(M+H) $^{+}$.) FN:FAB-MS(M-H) $^{-}$, EI:EI-MS (M^{+}), AP:APCI-MS(M+H) $^{+}$, MP : delta (ppm) of the characteristic peak in ^{1}H NMR in melting point (**) NMR1:$CDCl_3$, NMR2: delta (ppm) of the characteristic peak in ^{1}H NMR in DMSO-d_6, RT: HPLC(Wakosil-II 5C18AR 2.0 x 30 mm, 5 mM TFAaq / MeOH = 9/1(0 min)-0/10(7.5min)-0/10(8 min), 1.2 ml/min, 35 **, 254 the retention time (min) in nm, a Sal:salt, and a content solvent (Ox: -- an oxalate.) Fum: Fumaric acid chloride, a blank :. As for the number in front of a free object and an ingredient, for example, 2 HCl shows two hydrochlorides. Syn: -- a manufacturing method (a number shows the example number of manufacture manufactured similarly), and Me: -- methyl, Et:ethyl, iPr:2-propyl, cPr:cyclopropyl, tBu:t-butyl, cHex:cyclohexyl, and Ph:phenyl -- Bn:benzyl. Ac: Acetyl, Pip:piperidine- 1-yl, Pip4:piperidine- 4-yl, Mor:morpholine-4-yl, Pipr:piperazine 1-yl, Pyrr:pyrrolizine-1-yl, 4-Me-Pipr:4-methylpiperazine-1-yl. moreover -- the number in front of a substituent shows replacement positions -- for example, 2-Cl -- 2-chloro -- 3,4-diMe expresses 3,4-dimethyl, 2,3,4-triMe expresses 2,3,4-TORIMECHIRU, and 3,4- (OCH_2O) expresses a 3,4-methylenedioxy group, respectively.

MAC Science MXP18TAHF22 is used for measurement of a powder X diffraction, Bulb: It measured on conditions (Cu, tube current:120 mA, tube voltage:50 kV, sampling width:0.020 degree, scan speed:3 degrees /, min, wavelength:1.54056A, and measurement angle-of-diffraction range (2 theta):5-40 degree).

Thermometric analysis (DSC and TGA) was measured on the following conditions, respectively. DSC:TA Instrument TA 5000, room temperature -400 ** (10 ** / min), N2 (50 ml/min), the thump lupane made from aluminum. TGA:TA Instrument TA 5000, room temperature -400 ** (10 ** / min), N2 (100 ml/min), the thump lupane made from platinum.

[0044]

Reference example 1

Add palladium acetate, triphenyl phosphine, and sodium carbonate to the mixture of 6-chloropyridine- 2-methyl carboxylic acid, 3,4-dimethoxyphenylboric acid, dimethoxyethane, and water, and it reacts to it at 100 ** for 1 hour, 6-(3,4-dimethoxyphenyl) pyridine- 2-methyl carboxylic acid was obtained. Among the THF-methanol mixed solution, 1M sodium hydroxide solution was added, the obtained compound was reacted for 30 minutes under heating at 60 **, and 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid was obtained. NMR2: 8.18 (1H, d, J=8.0 Hz), 7.09 (1H, d, J=8.0 Hz), 3.87;(3H, s) F : 260.

Reference example 2

4-carbomethoxy benzophenone oxime which added hydroxylamine hydrochloride to the pyridine

solution of 4-methyl o-benzoylbenzoate, was made to react to it under heating, and was obtained, It was made to react among methanol and under palladium carbon existence and a hydrogen atmosphere, and 4-(alpha-aminobenzyl) methyl benzoate was obtained. F: 242.
Reference example 3
At -78 **, n-butyl lithium / n-hexane solution was added to the THF solution of the 4-bromo-2-chlorooanisole, and it stirred in it for 30 minutes. Subsequently, trimethyl borate was added, and to the room temperature, temperature up was carried out and it stirred for 30 minutes. The residue produced by distilling off a solvent was used instead of 3,4-dimethoxyphenylboric acid, and 6-(3-chloro-4-methoxypheny) pyridine- 2-carboxylic acid was obtained like the reference example 1. FN: 262.
[0045]
Reference example 4
6-(3-fluoro-4-methoxypheny) pyridine- 2-carboxylic acid was manufactured like the reference example 3. FN: 246.
Reference example 5
6-(3-benzyloxy 4-methoxypheny) pyridine- 2-carboxylic acid was manufactured like the reference example 3. NMR1: 6.95-7.05 (1H, m), 5.28 (2H, s), 3.95 (3H, s).
Reference example 6
6-(4-benzyloxy 3-methoxypheny) pyridine- 2-carboxylic acid was manufactured using 1-benzyloxy 4-bromo-2-methoxybenzene like the reference example 3 (however, hydrolysis was performed for 2.5 days at 100 ** among 1M sodium hydroxide solution). F: 336.
Reference example 7
Added concentrated hydrochloric acid and platinum oxide to the ethanol solution of N,N-diethylquinolin-2-carboxamide, it was made to react for bottom three days of a hydrogen atmosphere of 3 atmospheres, and N,N-diethyldecahydronaliumquinolin-2-carboxamide was obtained. F: 239.
Reference example 8
6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid and t-butoxycarbo NIRUPI perazine are used, Obtain a 1-{[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-(t-butoxycarbonyl) piperazine by the same method as the below-mentioned example 2 of manufacture, and add 4M hydrogen chloride / ethyl acetate solution further, and it reacts, The 1-{[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine was obtained. F: 328.
[0046]
Reference example 9
The bottom pyridine of ice-cooling and chloroacetyl chloride were made to add and react to the acetonitrile fluid of a 1-amino-1,2,3,4-tetrahydronaphthalene, and the 2-chloro-N-(1,2,3,4-tetrahydronaphthalene 1-yl) acetamide was obtained. Cesium carbonate and morpholine were added to the acetonitrile fluid of the obtained compound, it stirred at the room temperature for 17 hours, and the 2-(morpholine-4-yl)-N-(1,2,3,4-tetrahydronaphthalene 1-yl) acetamide was obtained. Lithium hydride aluminum was added to the THF solution of the obtained compound under ice-cooling, heating flowing back was carried out for 30 minutes, and N-[2-(morpholine-4-yl) ethyl]-1,2,3,4-tetrahydronaphthalene 1-ylamine was obtained as dihydrochloride. F: 261.
Reference example 10
To the toluene solution of 2-bromotoluene, 1-(t-butoxycarbonyl)-1,4-JIAZEPAN, Add tris(dibenzylidene acetone)dipalladium (0)2,2'-bis(diphenylphospino)-1,1'-binaphthyl and sodium t-butoxide, and it stirs at the oil bath temperature of 80 ** for 15 hours, 1-(t-butyloxy carbonyl)-4-(2-methylphenyl)-1,4-JIAZEPAN was obtained. 4M hydrogen chloride / ethyl acetate solution was added to the methanol solution of the obtained compound, it stirred at the room temperature for 4 hours, and 1-(2-methylphenyl)-1,4-JIAZEPAN was obtained as

dihydrochloride. F: 191.
Reference example 11
the acetic acid solution of 1-(ethoxycarbonyl) piperidine- 4-one -- 3-chloroaniline and hydrogenation -- doria -- SETOKISHIHOU -- base -- sodium was added, it stirred for 30 minutes at the room temperature, and the 4-(3-chlorophenylamino)-1-(ethoxycarbonyl) piperidine hydrochloride was obtained. Concentrated hydrochloric acid was added to the obtained compound, it stirred for two days at the oil bath temperature of 100 **, and 4-(3-chlorophenylamino) piperidine dihydrochloride was obtained. F: 211.
[0047]
Reference example 12
1-benzylisonipecotic acid ethyl was added to the THF solution of lithium diisopropylamide at -78 **, and it stirred at -78 ** for 1 hour. The methyl iodide was added to reaction mixture and it stirred for 30 minutes at -78 **, and it stirred for 1 hour, carrying out temperature up to a room temperature further gradually, and 1-benzyl-4-methyl isonipecotic acid ethyl was obtained. The obtained compound was stirred for 3.5 days at the oil bath temperature of 100 ** among 3M hydrochloric acid aqueous solution, and the 1-benzyl-4-methyl isonipecotic acid hydrochloride was obtained. Subsequently, the diphenyl azide phosphoryl and triethylamine were added among toluene, and heating flowing back of the obtained compound was carried out for 30 minutes. 2-(trimethylsilyl) ethanol was added to reaction mixture, it stirred at the oil bath temperature of 110 ** for 14 hours, and N-[2-(trimethylsilyl) ethoxycarbonyl]-1-benzyl-4-methyl-4-piperidyl amine was obtained. F: 349.
Reference example 13
1-benzyloxycarbonyl 4 -(t-butoxycarbonyl)- Using piperazine 2-carboxylic acid and morpholine, by the same method as the below-mentioned example 5 of manufacture. A 1-benzyloxycarbonyl 4-(t-butoxycarbonyl)-2-[(morpholine-4-yl) carbonyl] piperazine is obtained, Add 4M hydrogen chloride / ethyl acetate solution, it was made to react among ethyl acetate, and the 1-benzyloxycarbonyl 2-[(morpholine-4-yl) carbonyl] piperazine was obtained. This compound The inside of toluene, a bromobenzene, tris(dibenzylidene acetone)dipalladium (0), Under 2,2'-bis(diphenylphospino)-1,1'-binaphthyl and sodium t-butoxide existence, heating flowing back was carried out for one day, and 1-benzyloxycarbonyl 2-morpholino carbonyl 4-phenylpiperazine was obtained. The obtained compound was stirred for 1.5 days at the room temperature under the hydrogen atmosphere of ordinary pressure among ethanol and under 10% palladium carbon existence. The residue produced by distilling off a solvent was dissolved in ethanol after filtering out an insoluble matter, palladium carbon and ammonium formate were added 10%, it stirred for 2.5 days at the oil bath temperature of 70 **, and 2-[(morpholine-4-yl) carbonyl]-4-phenylpiperazine was obtained. F: 276.
[0048]
Reference example 14
CDI was added to the THF solution of 3-(t-butoxycarbonyl) amino-3-phenylpropanoic acid, and it stirred at the oil bath temperature of 60 ** for 3 hours. Morpholine was added after cooling to the room temperature, reaction mixture was stirred for one day at the room temperature, and N-(t-butoxycarbonyl)-2-[(morpholine-4-yl) carbonyl] 1-phenyl ethylamine was obtained. The obtained compound was stirred for 45 minutes at the room temperature among 4M hydrogen chloride / ethyl acetate solution, and 2-[(morpholine-4-yl) carbonyl]-1-phenyl ethylamine was obtained. F: 235.
Reference example 15
1-benzoylisonipecotic acid ethyl and ethyl bromoacetate are used, The 1-benzoyl-4-(ethoxy carbonylmethyl) isonipecotic acid ethyl obtained like the alkylation reaction of a statement to the reference example 12, It was made to react at 2 hours and also 80 ** with a room temperature

among ethanol and 1M sodium hydroxide solution for 18 hours, and 1-benzoyl-4-(carboxymethyl) isonipecotic acid was obtained. The trifluoroacetic anhydride was added to this compound and it stirred for 30 minutes at the room temperature. The residue produced by distilling off a solvent was dissolved in THF, morpholine was added, it stirred for 30 minutes at the room temperature, and 1-benzoyl-4-[(morpholine-4-yl) carbonylmethyl] isonipecotic acid was obtained. Furthermore, 1-benzoyl-N-(benzyloxycarbonyl)-4-[(morpholine-4-yl) carbonylmethyl]-4-piperidyl amine was obtained by the same method as the esterification reaction of a statement at ** for benzyl alcohol, and the reference example 12 instead of 2-(trimethylsilyl) ethanol. F: 466.

[0049]

Reference example 16

Add potassium carbonate and a benzyl bromide to the DMF solution of 4-bromo-2-ethylphenol, and it stirs for 30 minutes at the oil bath temperature of 60 **, Benzyl (4-bromo-2-ethylphenyl) ether was obtained, subsequently it processed like the first half of the reference example 3, and 6-(4-benzyloxy 3-ethylphenyl) pyridine- 2-methyl carboxylic acid was obtained. The inside of methanol of the obtained compound, and the mixed solution of THF, under 10% palladium carbon existence, The output acquired by stirring for 24 hours at the room temperature is dissolved in trifluoroacetic acid under the hydrogen atmosphere of ordinary pressure, The bottom pentamethylbenzene of ice-cooling was added, it stirred for 4.5 days at 1 hour and also a room temperature with the oil bath temperature of 50 **, and 6-(3-ethyl-4-hydroxyphenyl) pyridine- 2-methyl carboxylic acid was obtained. The obtained compound was processed with the trifluoromethanesulfonic anhydride among pyridine, and 6-(3-ethyl-4-trifluoromethane sulfonyloxy phenyl) pyridine- 2-methyl carboxylic acid was obtained.

In the 1,4-dioxane solution of the obtained compound, above Tributylvinyltin, A lithium chloride, tetrakis (triphenyl phosphine) palladium (0), and 2,6-di-tert-butyl-4-methylphenol were added, after carrying out heating flowing back for 18 hours, tetrakis (triphenyl phosphine) palladium (0) was added and heating flowing back was carried out for two days. Subsequently, potassium fluoride was added under the room temperature, it stirred for two days at the room temperature, and 6-(3-ethyl-4-vinylphenyl) pyridine- 2-methyl carboxylic acid was obtained. Process this compound in 1M sodium hydroxide solution among methanol, and consider it as 6-(3-ethyl-4-vinylphenyl) pyridine- 2-carboxylic acid, and also using 1-aminoindan by the same method as the below-mentioned example 5 of manufacture. 6-(3-ethyl-4-vinylphenyl)-N-Indang 1-yl pyridine- 2-carboxamide was obtained. F: 369.

[0050]

Reference example 17

In the DMF solution of 6-(3-ethyl-4-hydroxyphenyl) pyridine- 2-methyl carboxylic acid. Add potassium carbonate and a methyl iodide and it stirs at the oil bath temperature of 70 ** for 2 hours, 6-(3-ethyl-4-methoxypheny) pyridine- 2-methyl carboxylic acid was obtained, subsequently it stirred at the oil bath temperature of 60 ** among methanol and 1M sodium hydroxide solution for 1 hour, and 6-(3-ethyl-4-methoxypheny) pyridine- 2-carboxylic acid was obtained. F: 258.

Reference example 18

The phenyl(thiazole 2-yl) methanol which processed sequentially and obtained the thiazole with n-butyl lithium / n-hexane solution, and benzaldehyde among THF, It is made to react to manganese dioxide under heating among a toluene-dioxane mixed solvent, and is phenyl. (thiazole 2-yl) Ketone was obtained. Subsequently, it is made to react to hydroxylamine hydrochloride under heating among pyridine, and is phenyl. (thiazole 2-yl) Ketone Oxime was obtained. Added an ammonia solution and zinc dust, the obtained compound was made to react under heating among an ethanol water mixed solvent, and phenyl(thiazole 2-yl) methylamine

was obtained. EI: 190.
Reference example 19
6-chloropyridine- 2-methyl carboxylic acid, 4-methoxypheny boric acid, The mixture of sodium carbonate, tetrakis (triphenyl phosphino) palladium, dimethoxyethane, and water was made to react under heating, and 6-(4-methoxypheny) pyridine- 2-methyl carboxylic acid was obtained. The obtained compound was made to react to fuming nitric acid among an acetic anhydride, and 6-(4-methoxy-3-nitrophenyl) pyridine- 2-methyl carboxylic acid was obtained. It was made to react among the mixed solvent of THF, methanol, and 1M sodium hydroxide solution, and 6-(4-methoxy-3-nitrophenyl) pyridine- 2-carboxylic acid was obtained.
[0051]
Reference example 20
A benzyl bromide and potassium carbonate were added to the acetone solution of 2-bromophenol, it stirred under heating, and the 2-benzyloxy bromobenzene was obtained. Processed the obtained compound with the piece of magnesium in THF and under a little dibromoethane existence, subsequently it was made to react to pyridine- 4-carboxyaldehyde, and methanol (pyridin-(2-benzyloxyphenyl) 4-yl) was obtained. Hereafter, methylamine (pyridin-(2-benzyloxyphenyl) 4-yl) was obtained like the reference example 18. F: 291.
Reference example 21
4-iodophenol was made to react to 2-dimethylaminoethanehydrochloride chloride under heating under existence of potassium carbonate among DMF, and [2-(4-iodophenoxy) ethyl] dimethylamine was obtained. The obtained compound Piperazine 1-carboxylic acid t-butylester, Under the tris(dibenzylidene acetone)dipalladium (0) existence of sodium t-butoxide, the Tori (2-methylphenyl) phosphine, and a catalyst amount, It was made to react among toluene and under heating, and 4-[4-(2-dimethylamino ethoxy) phenyl] piperazine 1-carboxylic acid t-butyl was obtained. F: 350.
Reference example 22
1-benzylpyrrolidine 3-one and N-(2-aminoethyl) morpholine -- hydrogenation among acetic acid -- doria -- SETOKISHIHOU -- base -- it was made to react to sodium at a room temperature, and amine (2(1-benzylpyrrolidine 3-yl)-morpholine-4-yl ethyl) was obtained. F: 290.
[0052]
Reference example 23
Added potassium carbonate to the DMF solution of 2-cyanophenol and 4-(2-chloroethyl) morpholine hydrochloride, it was made to react to it under heating, and 4-[2-(2-cyanophenoxy) ethyl] morpholine was obtained. The obtained compound was made to react to lithium hydride aluminum under heating among THF, and 4-[2-(2-aminomethyl phenoxy) ethyl] morpholine was obtained. F: 237.
Reference example 24
2,6-dichloro pyrazine was made to react to bottom piperazine of existence of potassium carbonate 1-carboxylic acid t-butylester under heating among N,N-dimethylimidazolidinone, and 2-chloro-6-(4-t-butoxycarbo NIRUPI perazine 1-yl) pyrazine was obtained. F: 299.
Reference example 25
6-(3-benzyloxy 4-methoxypheny) pyridine- 2-methyl carboxylic acid was stirred among a THF-methanol mixed solvent and under palladium carbon existence and a hydrogen atmosphere, and 6-(3-hydroxy-4-methoxypheny) pyridine- 2-methyl carboxylic acid was obtained. The obtained compound is made to react to cyclopropyl methyl bromide and potassium carbonate under heating among DMF, 6-(3-cyclopropylmethoxy-4-methoxypheny) pyridine- 2-methyl carboxylic acid is obtained, Added 1M sodium hydroxide solution, it was made to react under heating among a THF-methanol mixed solvent, and 6-(3-cyclopropylmethoxy-4-methoxypheny) pyridine- 2-carboxylic acid was obtained. FN: 294.

[0053]
Reference example 26
6-(3-difluoromethoxy-4-methoxypheny) pyridine- 2-carboxylic acid was manufactured like the reference example 25. NMR1: 7.93-8.00 (2H, m), 7.01 (1H, d, J=8.0 Hz), and 1.35-1.42 (1H, m).
Reference example 27
It is acetic acid (4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) like the reference example 25. Ethyl was manufactured. F: 506.
Reference example 28
It is 5-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) pentanoic acid like the reference example 25. Methyl was manufactured. F: 534.
Reference example 29
It is 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) butanoic acid like the reference example 25. Ethyl was manufactured. F: 534.
Reference example 30
It is 6-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) hexanoic acid like the reference example 25. Ethyl was manufactured. F:562.
Reference example 31
It is 7-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) heptanoic acid like the reference example 25. Ethyl was manufactured. F: 576.
Reference example 32
It is 4-(3-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) butanoic acid like the reference example 25. Ethyl was manufactured. F: 534.
Reference example 33
It is 5-(3-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) pentanoic acid like the reference example 25. Methyl was manufactured. F: 534.
Reference example 34
It is 6-(3-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) hexanoic acid like the reference example 25. Ethyl was manufactured. F: 562.
Reference example 35
It is 4-(2-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) butanoic acid like the reference example 25. Ethyl was manufactured. F: 534.
Reference example 36
It is 5-(2-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) pentanoic acid like the reference example 25. Methyl was manufactured. F: 534.
Reference example 37
It is 6-(2-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) hexanoic acid like the reference example 25. Ethyl was manufactured. F: 562.
Reference example 38
1-(t-butoxycarbonyl)-4-[2-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) ethyl] piperazine was manufactured like the reference example 25. F: 632.
Reference example 39
It is 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} anilino) butanoic acid like the reference example 25. Ethyl was manufactured. F: 533.
[0054]
Reference example 40
The thionyl chloride was added to 6-chloronicotinic acid, and heating flowing back was carried out. After cooling to a room temperature, it condensed under decompression. Benzene and an aluminium chloride were added and heating stirring was carried out at 100 **. Sodium methoxide was added to the DMF solution of the 2-chloro-5-benzoylpyridine produced by

carrying out post-processing refining with the conventional method below, and heating stirring was carried out. Post-processing refining was carried out with the conventional method below, and 2-methoxy-5-benzoylpyridine was obtained. NMR1: 8.62-8.63 (1H, m), 7.77-7.80 (2H, m), and 4.03 (3H,d,J=1.2Hz).

Reference example 41

It is 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine like the example 5 of the after-mentioned manufacture. A little salt acid chloride was obtained. F:328.

Reference example 42

It is 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenylcarbamoyl) piperidine- 1-carboxylic acid like the example 5 of the after-mentioned manufacture. Benzyl was obtained. F:664.

Reference example 43

It is (**)-trans-3-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-2,5-dimethylpiperazine 1-yl} phenyl) propionic acid like the example 5 of the after-mentioned manufacture. Ethyl was obtained. F: 532.

Reference example 44

It is (**)-trans-5-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-2,5-dimethylpiperazine 1-yl} phenyl) pentanoic acid like the example 5 of the after-mentioned manufacture. Ethyl was obtained. F: 560.

[0055]

Reference example 45

To the toluene solution of a 4-bromo-2-chloroanisole, it is 1. -(t-butoxycarbonyl)- Piperazine, Tris(dibenzylidene acetone)dipalladium (0)2,2'-bis(diphenylphospino)-1,1'-binaphthyl and sodium t-butoxide was added, and it stirred at the oil bath temperature of 110 ** for 4 hours. Post-processing refining was carried out with the conventional method below, and the 1-(t-butoxycarbonyl)-4-(3-chloro-4-methoxypheny) piperazine was obtained. NMR1: 6.99 (1H,d,J=2.8Hz), 3.85 (3H, s), and 1.48 (9H, s).

Reference example 46

The 1-(t-butoxycarbonyl)-4-(3-fluoro-4-methoxypheny) piperazine was obtained like the reference example 45. NMR1: 6.72 (1H, dd, J = 14 or 2.8 Hz), 3.85 (3H, s), and 1.48 (9H, s).

Reference example 47

The 1-(benzofuran-5-yl)-4-(t-butoxycarbonyl) piperazine was obtained like the reference example 45. NMR1: 7.58 (1H,d,J=2.4Hz), 3.07-3.09 (4H, m), and 1.49 (9H, s).

Reference example 48

The 1-(t-butoxycarbonyl)-4-(4-diethylaminophenyl) piperazine was obtained like the reference example 45. F: 334.

[0056]

Reference example 49

Trifluoroacetic acid was added to the chloroform fluid of the 1-(t-butoxycarbonyl)-4-(3-chloro-4-methoxypheny) piperazine, and it stirred for 30 minutes. Post-processing refining was carried out with the conventional method below, and 1-(3-chloro-4-methoxypheny) piperazine was obtained. F: 227.

Reference example 50

1-(3-fluoro-4-methoxypheny) piperazine was obtained like the reference example 49. F: 211.

Reference example 51

1-(3-chloro pyrazine 2-yl) piperazine was obtained like the reference example 49. NMR2: 8.26 (1H,d,J=2.4Hz), 7.97 (1H,d,J=2.4Hz), and 2.81-2.84 (4H, m).

Reference example 52

Diethyl (4-piperazino phenyl) amine was obtained like the reference example 49. F: 234.

Reference example 53
It is (**)-trans-3-[4-(2,5-dimethylpiperazine 1-yl) phenyl] propionic acid like the reference example 49. Ethyl was obtained. F: 291.
Reference example 54
It is (**)-trans-5-[4-(2,5-dimethylpiperazine 1-yl) phenyl] pentanoic acid like the reference example 49. Ethyl was obtained. F: 319.
Reference example 55
1-(5-methoxy pyridin-3-yl) piperazine was obtained like the reference example 45 and the reference example 49. NMR1: 7.96 (1H, d, J=2.4 Hz), 7.82 (1H, d, J=2.4 Hz), and 3.84 (3H, s).
Reference example 56
1-(6-methoxy pyridin-3-yl) piperazine was obtained like the reference example 45 and the reference example 49.
Reference example 57
6-piperazine 1-yl quinoline was obtained like the reference example 45 and the reference example 49. EI: 213.
Reference example 58
1-(6-bromopyridin-2-yl) piperazine was obtained like the reference example 45 and the reference example 49. F: 242.
Reference example 59
1-(5-bromopyridin-2-yl) piperazine was obtained like the reference example 45 and the reference example 49. F: 242.
[0057]
Reference example 60
The NMP solution of 6-chloronicotinonitrile and a (**)-trans-2,5-dimethylpiperazine was stirred at the oil bath temperature of 120 ** for 1 hour, and (**)-trans-6-(2,5-dimethylpiperazine 1-yl) nicotinonitrile was obtained. F: 217.
Reference example 61
1-(4-piperazine 1-yl- 2-trifluoro methylphenyl) ethanone was obtained like the reference example 60. F: 273.
Reference example 62
(**)-trans-1-[4-(2,5-dimethylpiperazine 1-yl) phenyl]ethanone was obtained like the reference example 60. F: 233.
Reference example 63
1-(2-hydroxy-4-piperazine 1-yl phenyl) ethanone was obtained like the reference example 60. F: 221.
Reference example 64
1-(5-nitropyridin-2-yl) piperazine was obtained like the reference example 60. F: 209.
Reference example 65
(**)-trans-4-(2,5-dimethylpiperazine 1-yl) benzaldehyde was obtained like the reference example 60. F: 219.
[0058]
Reference example 66
Potassium carbonate was added to the NMP solution of 4-fluorobenzaldehyde and 1-(t-butoxycarbonyl) piperazine, and heating stirring was carried out. Post-processing refining was carried out with the conventional method below, and 4-[4-(t-butoxycarbonyl) piperazine 1-yl] benzaldehyde was obtained. NMR1: 9.80 (1H, s), 3.37-3.40 (4H, m), and 1.49 (9H, s).
Reference example 67
2-chloro-3-(4-t-butoxycarbo NIRUPI perazine 1-yl) pyrazine was obtained like the reference example 66. NMR1: 7.91 (1H,d,J=2.4Hz), 3.58-3.61 (4H, m), and 1.49 (9H, s).

Reference example 68
The 1-(4-acetyl-2-chlorophenyl)-4-(t-butoxycarbonyl) piperazine was obtained like the reference example 66. NMR1: 7.07 (1H,d,J=8.8Hz), 3.08-3.12 (4H, m), and 1.49 (9H, s).
Reference example 69
6-[4-(t-butoxycarbonyl) piperazine 1-yl] pyridine- 3-carbaldehyde was obtained like the reference example 66. NMR1: 9.80 (1H, s), 3.54-3.58 (4H, m), and 1.49 (9H, s).
Reference example 70
6-[4-methylpiperazine-1-yl] pyridine- 3-carbaldehyde was obtained like the reference example 66. NMR1: 9.78 (1H, s), 6.66 (1H,d,J=8.0Hz), and 2.35 (3H, s).
Reference example 71
At 150 **, 2-chlorobenzo thiazole was added to the piperazine which carried out melting, and it stirred for 1 hour. Post-processing refining was carried out with the conventional method below, and the piperazine (benzothiazole 2-yl) was obtained. F: 220.
[0059]
Reference example 72
Diethylphosphonoethyl acetate was dropped at sodium hydride and a THF mixture under 0 ** cooling 60%, and also 4-[4-(t-butoxycarbonyl) piperazine 1-yl] benzaldehyde was dropped, and it stirred. Post-processing refining was carried out with the conventional method below, and 3-{4-[4-(t-butoxycarbonyl) piperazine 1-yl] phenyl} ethyl acrylate was obtained. 4-[4-(t-butoxycarbonyl) piperazine 1-yl] ethyl 3-{phenyl}propanoate was obtained like the after-mentioned reference example 94. NMR1: 4.12 (2H,q,J=7.2Hz), 2.87 (2H,t,J=7.6Hz), and 1.48 (9H, s).
Reference example 73
3-{6-[4-(t-butoxycarbonyl) piperazine 1-yl] pyridin-ethyl 3-yl}propanoate was obtained like the reference example 72. NMR1: 6.60 (1H, d, J= 8.8 Hz), 4.12 (2H, q, J= 7.2 Hz), and 2.56 (2H, t, J= 7.6 Hz).
Reference example 74
(**)-trans-3-{4-[1-(t-butoxycarbonyl)-2,5-dimethylpiperazine 4-yl]phenyl} propanoate was obtained like the reference example 72. [ethyl] EI: 390.
[0060]
Reference example 75
By the same method as the reference example 49 and the example 5 of the after-mentioned manufacture, 3-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) ethyl propanoate was obtained. NMR1:6.97 (1H, d, J= 8.4 Hz), 4.12 (2H, q, J= 7.2 Hz), and 2.89 (2H, t, J= 7.6 Hz).
Reference example 76
5-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) ethyl pentanoate was obtained like the reference example 75. NMR1: 6.97 (1H, d, J= 8.8 Hz), 4.12 (2H, q, J= 7.2 Hz), and 2.31 (2H, t, J= 7.2 Hz).
Reference example 77
3-(6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyridin-3-yl) ethyl propanoate was obtained like the reference example 75. NMR1: 6.97 (1H, d, J= 8.8 Hz), 4.12 (2H, q, J= 7.2 Hz), and 2.84 (2H, t, J= 7.6 Hz).
Reference example 78
The DMSO solution of 6-chloro-methyl nicotinate and a piperazine was stirred at the oil bath temperature of 120 **, and the 6-piperazine 1-yl methyl nicotinate was obtained. F: 222.
Reference example 79
By the reaction more nearly same than 2-nitro 5-fluorophenol as the reference example 25 and the reference example 66, the 1-(3-benzyloxy 4-nitrophenyl)-4-(t-butoxycarbonyl) piperazine

was obtained. NMR1: 8.01 (1H,d,J=8.4Hz), 5.22 (2H, s), and 1.49 (9H, s).
[0061]
Reference example 80
Palladium carbon was added to the methanol THF mixed solution of the 1-(3-benzyloxy 4-nitrophenyl)-4-(t-butoxycarbonyl) piperazine, and it stirred under a hydrogen atmosphere. Methyl orthoformate and p-toluenesulfonic acid were added to the methanol solution of the 2-amino-5-[1-(t-butoxycarbonyl) piperazine 4-yl] phenol produced by carrying out post-processing refining with a conventional method below, and heating stirring was carried out. Post-processing refining was carried out with the conventional method below, and 6-(4-t-butoxycarbo NIRUPI perazine 1-yl) benzooxazol was obtained. NMR1: 7.97 (1H, s), 3.15-3.19 (4H, m), and 1.49 (9H, s).
Reference example 81
By the method more nearly same than 4,6-dichloropyrimidine as the reference example 60 and the reference example 49, 4-chloro-6-piperazine 1-yl pyrimidine was obtained. F: 199.
Reference example 82
N-benzyliminodiacetic acid is made to react to CDI and 5-aminoindole among THF, and 4-benzyl-1-(1H-indole- 5-yl) piperazine 2,6-dione was obtained, and, subsequently it was made to react to lithium hydride aluminum among THF. Added concentrated hydrochloric acid and hydroxylation palladium to the ethanol solution of the obtained compound, it was made to react under a 3-atmosphere hydrogen atmosphere for 65 hours, and 5-piperazine 1-yl- 1H-Indore was obtained. EI: 201.
Reference example 83
4-(2-chloropyrimidine 4-yl) piperazine 1-carboaldehyde and 2-(dimethylamino) ethanol Under potassium t-butoxide existence, The compound produced by reacting among DMF was made to react at 80 ** under potassium carbonate existence into methanol for 24 hours, and N,N-dimethyl- N-{2-[(4-piperazine 1-yl pyrimidine-2-yl) oxy] ethyl} amine was obtained. F: 252.
[0062]
Reference example 84
4-[4-(t-butoxycarbonyl) piperazine 1-yl] benzaldehyde and [3-(ethoxycarbonyl) propyl] triphenyl phosphonium bromide, Make it react under t-butoxypotassium existence in THF, obtain 5-{4-[4-(t-butoxycarbonyl) piperazine 1-yl] phenyl}-4-pentene acid ethyl, and it ranks second, 4-[4-(t-butoxycarbonyl) piperazine 1-yl] ethyl 5-{phenyl}pentanoate was obtained like the after-mentioned reference example 94. NMR1: 4.12 (2H,q,J=7.2Hz), 2.31 (2H,t,J=7.2Hz), and 1.48 (9H, s).
Reference example 85
5-(6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyridin-3-yl) ethyl pentanoate was obtained like the reference example 84. NMR1: 8.02 (1H,d,J=2.4Hz), 4.12 (2H,q,J=7.2Hz), and 1.48 (9H, s).
Reference example 86
The (**)-trans-1-(t-butoxycarbonyl)-4-[4-(4-ethoxycarbonylbutyl) phenyl]-2,5-dimethylpiperazine was obtained like the reference example 84. FN: 417.
Reference example 87
Make a 2-bromo-6-iodopyridin-3-oar react to potassium carbonate and a benzyl bromide, obtain 3-(benzyloxy)-2-bromo-6-iodopyridine, and it ranks second, It processed sequentially like the reference example 45, the example 43 of manufacture, the example 5 of manufacture, and the reference example 94, and the 6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyridin-3-oar was obtained. F: 421.
[0063]
Reference example 88

60% sodium hydride and ethyl 4-bromobutanoate was added to the DMF solution of the 2-bromo-6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyridin-3-oar, and it was made to react to it at a room temperature for 1 hour. Post-processing refining was carried out with the conventional method below, and ethyl 4-[(2-bromo-6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl}-3-pyridyl) oxy]butanoate was obtained. F: 535.

Reference example 89

It processes sequentially by the method more nearly same than 4-(2-chloropyrimidine 4-yl) piperazine 1-carboaldehyde and benzyl alcohol as the reference example 83, the example 5 of manufacture, the reference example 94, and the reference example 88, 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl}-2-oxo 1,2-dihydropyrimidine 1-yl) ethyl butanoate was obtained. F: 536.

Reference example 90

1,2-dibromoethane, 2M sodium hydroxide solution, tetra-n-butyl ammonium hydrogensulfate, and water were added to the 4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-1-(4-hydroxyphenyl) piperazine, and it stirred at 60 **. Water and chloroform were added after cooling reaction mixture, and the insoluble matter was filtered out. Post-processing refining was carried out with the conventional method below, and the 1-[4-(2-bromoethoxy) phenyl]-4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine was obtained. F: 526.

[0064]

Reference example 91

Add potassium t-butoxide to the DMF solution of 2,5-dibromopyridine and 2-(dimethylamino) ethanol, and it stirs at the oil bath temperature of 100 ** for 3 hours, N-{2-[(5-bromopyridin-2-yl) oxy] ethyl}-N,N-dimethylamine was obtained, and also N,N-dimethyl- N-{2-[(5-piperazine 1-yl pyridin-2-yl) oxy] ethyl} amine was obtained like the reference example 55. F: 251.

Reference example 92

Using 2-(benzyloxy)-6-bromonaphthalene, it processed sequentially like the reference example 45, the example 43 of manufacture, and the example 5 of manufacture, and the 1-[6-(benzyloxy)-2-naphthyl]-4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine was obtained. This compound was dissolved in trifluoroacetic acid, the bottom pentamethylbenzene of ice-cooling was added, it stirred at 2 hours and also the oil bath temperature of 40 ** with the room temperature for 2 hours, and 6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl}-2-naphthol was obtained. F: 470.

Reference example 93

Palladium acetate triphenyl phosphine, methyl acrylate, and cesium carbonate were added to the dioxan solution of 6-pyridine- 3-carboxaldehyde, and heating flowing back was carried out. Post-processing refining was carried out with the conventional method below, and 3-(5-formylpyridin-2-yl) methyl acrylate was obtained. NMR1: 10.13 (1H, s), 7.08 (1H,d,J=15.6Hz), and 3.85 (3H, s).

[0065]

Reference example 94

Palladium carbon was added to the ethyl acetate ethanol solution of 3-(5-formylpyridin-2-yl) methyl acrylate, and it stirred under a hydrogen atmosphere. Post-processing refining was carried out with the conventional method below, and 3-(5-formylpyridin-2-yl) methyl propanoate was obtained. NMR1: 10.29 (1H, s), 3.68 (3H, s), and 2.88 (2H,t,J=7.2Hz).

Reference example 95

JI (t-butoxycarbonyl) dicarbo NETO and 4-dimethylaminopyridine were added and stirred to the acetonitrile fluid of (**)-trans-4-(2,5-dimethylpiperazine 1-yl) benzaldehyde. Post-processing refining was carried out with the conventional method below, and (**)-trans-1-(t-butoxycarbonyl)-4-(4-formylphenyl)-2,5-dimethylpiperazine 1-carboxylic acid t-butyl was

obtained. F: 319.
Reference example 96
The NMP solution of fluoro-4-nitrobenzene and a (**)-trans-2,5-dimethylpiperazine is stirred at the oil bath temperature of 120 ** for 3 hours, Obtain a (**)-trans-2,5-dimethyl- 1-(4-nitrophenyl) piperazine, and also it is made to be the same as that of the example 5 of manufacture, The (**)-trans-1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-2,5-dimethyl- 4-(4-nitrophenyl) piperazine was obtained. F: 477.
Reference example 97
6-chloroquinoline Added 3-oxobutyric acid methyl to the acetic anhydride solution of 1-oxide, added to chloride the compound obtained by stirring for 30 minutes at the oil bath temperature of 40 ** 10%, it was made to react at a room temperature, and methyl acetate (6-chloroquinolin-2-yl) was obtained. this -- a compound -- further -- a reference example -- 45 -- manufacture -- an example -- 43 -- and -- manufacture -- an example -- five -- the same -- processing sequentially -- six - {-- four - [-- six - (3,4-dimethoxyphenyl) -- pyridine- -- two - carbonyl --] -- a piperazine -- one - an yl --} -- quinolin- -- two - an yl --] -- methyl acetate -- having obtained . F: 527.
Reference example 98
It is 4-[N-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl)-N-methylamino] butanoic acid like the example 10 of the after-mentioned manufacture. Ethyl was obtained. F: 547.
[0066]
The example 1 of manufacture
2-oxo 3-phenylpiperazine Lithium hydride aluminum 638 mg was added to the THF 20 ml solution of 740 mg, and heating flowing back was carried out for 3 hours. Reaction mixture was ice-cooled, and the insoluble matter was filtered out, after, stirring sodium sulfate 10 hydrate for a while in addition until gel was lost in reaction mixture. About crude 2-phenylpiperazine which distilled off and obtained the solvent, it is 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid. It adds to the THF 20 ml solution of 500 mg, and also is a WSC hydrochloride. 556 mg and HOBt 260 mg were added, and it stirred for two days at the room temperature. Ethyl acetate was added to reaction mixture, water and a saturation salt solution washed, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Silica gel column chromatography (chloroform methanol) refined the obtained residue, and the colorless amorphous crystal (670 mg) was obtained. This compound is dissolved in ethanol and it is fumaric acid. After adding 192 mg and considering it as fumaric acid chloride, Recrystallization is performed from ethanol ethyl acetate and it is 2-(3,4-dimethoxyphenyl)-6-(3-phenylpiperazine 1-carbonyl) pyridine. 0.5 fumaric acid chloride 607 mg was obtained as a colorless crystal.
The example 2 of manufacture
6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid Oxalyl chloride 0.18 ml and DMF 1 drop were added to the THF 20 ml solution of 500 mg under ice-cooling. It is 4-(4-methoxypheny) piperazine after 30-minute stirring and about reaction mixture. Pyridine of 370 mg It was dropped at 10 ml solution under ice-cooling. Temperature up was carried out to the room temperature, and also it stirred for 30 minutes. Water was added to reaction mixture and ethyl acetate extracted. The saturation salt solution washed the organic layer and the after-desiccation solvent was distilled off with anhydrous magnesium sulfate. Silica gel column chromatography (chloroform methanol) refines residue, Recrystallization is performed from ethyl acetate acetonitrile and it is a 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-(4-methoxypheny) piperazine. 370 mg was obtained as a colorless crystal.
[0067]
The example 3 of manufacture
4-[4-(2-dimethylamino ethoxy) phenyl] piperazine 1-carboxylic acid t-butyl They are 4M

hydrogen chloride / ethyl acetate solution about 0.62 g. It was made to react among 15 ml. Rough product produced by distilling off a solvent To the DMF 15 ml solution of 0.86 g, it is a WSC hydrochloride. 0.34 g, HOBt 0.24 g, and 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid 0.41 g was added and it was made to react under a room temperature for 65 hours. WSC hydrochloride 0.34 g, HOBt 0.24 g, and triethylamine 0.50 ml was added and it stirred under the room temperature for 8.5 hours. Water was added to reaction mixture and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. It is oxalic acid about the compound obtained after refining with silica gel column chromatography (ethyl acetate) in residue. Carry out salt formation by 106 mg, and it recrystallizes (ethanol), 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-[4-(2-dimethylamino ethoxy) phenyl] piperazine 2 oxalates 253 mg was obtained as a light yellow crystal.

The example 4 of manufacture

1-benzyl-4-benzoylpiperidine Pyridine of 4.50 g To 50 ml solution, it is hydroxylamine hydrochloride. 3.00 g was added and it stirred at the oil bath temperature of 80 ** for 1 hour. 1M sodium hydroxide solution was added after cooling to the room temperature, and chloroform extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. 1-benzyl piperidine- 4-yl which washed and obtained residue with diisopropyl ether Phenyl Ketone Oxime 3.50 g is dissolved in THF 50 ml, and it is lithium aluminum hydride at the oil bath temperature of 60 **. 6.50 g was added gradually. It heated at the oil bath temperature of 80 ** after 30-minute stirring then for 30 minutes. The bottom of ice-cooling, methanol 10 ml and anhydrous sodium sulfate were added one by one. The insoluble matter was filtered, water was added to filtrate, and ethyl acetate extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. 4-(alpha-aminobenzyl)-1-benzylpiperidine which refined and obtained residue with silica gel column chromatography (chloroform methanol) 1.03 g, Using 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid 1.00 g, by the same method as the example 2 of manufacture. N-[(1-benzyl piperidine- 4-yl) (phenyl) methyl]-6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide 620 mg was obtained as a colorless crystal. [0068]

The example 5 of manufacture

6 -(3,4-dimethoxyphenyl)- Pyridine- 2-carboxylic acid 1.20 g, Phenyl(pyridin-4-yl) methylamine To the DMF 20 ml solution of 850 mg, it is a WSC hydrochloride. 960 mg, HOBt 800mg, and triethylamine 0.72 ml was added at the room temperature. Water was added after 2-hour stirring and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and it dried with anhydrous magnesium sulfate. Silica gel column chromatography (chloroform methanol) refines residue after distilling off a solvent, Recrystallization is performed from ethyl acetate and it is 6-(3,4-dimethoxyphenyl)-N-[phenyl(pyridin-4-yl) methyl] pyridine- 2-carboxamide. 1.25 g was obtained as a colorless crystal.

The example 6 of manufacture

6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid It is an oxalyl chloride to the THF 5 ml solution of 500 mg. 0.34 ml and DMF of the catalyst amount were added, and it stirred at the room temperature for 1 hour. The solvent of reaction mixture is distilled off and it is acetonitrile about residue. It is considered as 10 ml solution and is a 2,2-diphenylglycine. 440 mg, triethylamine 0.80 ml, and 4-(dimethylamino) pyridine 24 mg was added and it stirred at the room temperature for 16 hours. The insoluble matter was separated, it washed by ethanol, and the colorless crystal (199 mg) was obtained. 1M hydrochloric acid aqueous solution was added to this compound, and chloroform extracted. The saturation salt solution washed the organic layer, it dried with anhydrous magnesium sulfate, and the solvent was distilled off. Acetonitrile

and diisopropyl ether wash the obtained rough crystal one by one, and it is {[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] Amino} (diphenyl) acetic acid. 119 mg was obtained as a colorless crystal.

[0069]

The example 7 of manufacture

6-(3,4-dimethoxyphenyl)-N-[(2-benzyloxyphenyl) (pyridin-4-yl) methyl] pyridine- 2-carboxamide It is trifluoroacetic acid about 5.25 g. It is made to dissolve in 40 ml, Pentamethylbenzene It stirred for five days at 4.39 g and room temperature -50 **. Sodium bicarbonate solution was added after distilling off reaction mixture, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Silica gel column chromatography (chloroform ethanol) refines residue, It recrystallizes (2-propanol) and is 6-(3,4-dimethoxyphenyl)-N-[(2-hydroxyphenyl) (pyridin-4-yl) methyl] pyridine- 2-carboxamide. 1.028 g was obtained as a colorless crystal.

The example 8 of manufacture

6-(3,4-dimethoxyphenyl)-N-[(2-hydroxyphenyl) (pyridin-4-yl) methyl] pyridine- 2-carboxamide 0.25 g is dissolved in DMF 5 ml, Potassium carbonate The bottom of 0.15 g existence, methyl iodide It was made to react to 40 ml at a room temperature for 5 hours. Water was added to reaction mixture and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. It recrystallizes, after processing and carrying out salt formation of the compound obtained by silica gel column chromatography (ethyl acetate) refining residue with 4M hydrogen chloride / ethyl acetate solution (ethanol), 6-(3,4-dimethoxyphenyl)-N-[(2-methoxypheny) (pyridin-4-yl) methyl] pyridine- 2-carboxamide A little salt acid chloride 157 mg was obtained as a colorless crystal.

[0070]

The example 9 of manufacture

N-(1-benzyl-4-phenyl piperidine- 4-yl)-6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide Dichloroethane of 250 mg 0.18 ml of chloroformic acid 1-chloroethyl was added to 3 ml solution at the room temperature. After stirring for 30 minutes, the solvent was distilled off, 10 ml of methanol was added, and it stirred for 30 minutes. 3M chloride was added and it was considered as basicity by 1M sodium hydroxide after washing with ether. Chloroform extracted, the saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. The output (150 mg) which refined and obtained residue with silica gel column chromatography (chloroform methanol) is dissolved in methanol, and it is fumaric acid. 40 mg was added and the solvent was distilled off. The obtained rough crystal is ******ed from acetonitrileethanol and it is 1 fumaric acid chloride of 6-(3,4-dimethoxyphenyl)-N-(4-phenyl piperidine- 4-yl) pyridine- 2-carboxamide. 1.5 hydrates 53 mg was obtained as a colorless crystalline solid.

The example 10 of manufacture

Methanol of 6-(3,4-dimethoxyphenyl)-N-(4-phenyl piperidine- 4-yl) pyridine- 2-carboxamide 500 mg In 10 ml solution. 35% formalin aqueous solution 0.5 ml and acetic acid 0.5 ml and doria -- SETOKISHI sodium borohydride 300 mg was added. after 30-minute stirring and also doria -- SETOKISHI sodium borohydride 100 mg was added and it stirred for 30 minutes. 1M sodium hydroxide solution was added and ethyl acetate extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. The output (440 mg) which refined and obtained residue with silica gel column chromatography (chloroform methanol ammonia solution) is dissolved in methanol, and it is fumaric acid. 120 mg was added and the solvent was distilled off. recrystallizing [ethanol /

acetonitrile] -- 6-(3,4-dimethoxyphenyl)- N-(1-methyl-4-phenyl piperidine- 4-yl) pyridine- 2-carboxamide 1 fumaric acid chloride 390 mg was obtained as a colorless crystal.
[0071]
The example 11 of manufacture
N-[2-(trimethylsilyl) ethoxycarbonyl]-1-benzyl-4-methyl-4-piperidyl amine 1,4-dioxane of 1.35 g In 15 ml solution. 1M tetrabutylammonium fluoride / THF solution 5.0 ml was added and it stirred at the oil bath temperature of 70 ** for 13 hours. 1M tetrabutylammonium fluoride / THF solution 2.0 ml was added and it stirred for one day at the oil bath temperature of 70 **. Ethyl acetate was added to the residue produced by distilling off the solvent of reaction mixture, and 1M hydrochloric acid aqueous solution extracted. After sodium bicarbonate neutralized the water layer, chloroform extracted. The organic layer was dried with anhydrous sodium sulfate, the solvent was distilled off, and crude 1-benzyl-4-methyl piperidine 4-ylamine was obtained. It is N-(1-benzyl-4-methyl-4-piperidyl)-6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide like an amidation reaction given in the example 1 of manufacture hereafter using this compound. 1 oxalate 450 mg was obtained as a colorless crystal.
The example 12 of manufacture
1-benzoyl-N-(benzyloxycarbonyl)-4-(morpholine 4-yl-carbonyl methyl) piperidine- 4-ylamine Ethanol of 800 mg In 20 ml solution. 10% palladium carbon 80 mg and ammonium formate 300 mg was added and it stirred at the oil bath temperature of 70 ** for 17 hours. An insoluble matter is filtered out of reaction mixture, a solvent is distilled off, and it is crude 1-benzoyl-4-(morpholine 4-yl-carbonyl methyl) piperidine- 4-ylamine. 549 mg was obtained as a light yellow oily matter. Under heating flowing back of lithium hydride aluminum 400 mg and a THF 10 ml mixture, the THF 5 ml solution of the obtained compound was dropped, and heating flowing back was carried out for 30 minutes as it was. Reaction mixture was ice-cooled, and in addition, the after-stirring insoluble matter was filtered out for a while until gel was lost in reaction mixture in sodium sulfate 10 hydrate. A solvent is distilled off and it is crude 1-benzyl-4-[2-(morpholine-4-yl) ethyl] piperidine- 4-ylamine. 427 mg was obtained as a light yellow oily matter.
6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid To the THF 5 ml solution of 360 mg, it is an oxalyl chloride. 0.25 ml and DMF of the catalyst amount were added, and it stirred for 15 minutes at the room temperature. 1-benzyl-4-[2-(morpholine-4-yl) ethyl] piperidine- 4-ylamine and triethylamine which dissolved the residue produced by distilling off a solvent in THF 10 ml, and were obtained previously 0.50 ml was added and it stirred at the room temperature for 14 hours. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. The saturation salt solution washed the organic layer, it dried with anhydrous magnesium sulfate, and the solvent was distilled off. Silica gel column chromatography (chloroform methanol) refined the obtained residue, and the yellow amorphous crystal (415 mg) was obtained. This compound is dissolved in methanol and it is fumaric acid. It recrystallizes [isopropanol], after adding 176 mg and considering it as fumaric acid chloride, N-[-- 1-benzyl-4-{[2-(morpholine-4-yl) ethyl] piperidine- 4-yl}-6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide 2 fumaric acid chloride monohydrate 364 mg was obtained as a colorless crystal.
[0072]
The example 13 of manufacture
1-benzyl-4-{[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] Amino} piperidine- 4-methyl carboxylic acid It is sodium borohydride to the THF 30 ml solution of 1.70 g. 500 mg was added. It is methanol at the oil bath temperature of 70 **. 5 ml was dropped and it stirred for 30 minutes. Water was added after cooling to the room temperature, and ethyl acetate extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with magnesium sulfate. Silica gel column chromatography (chloroform methanol)

refines residue, and also it recrystallizes (isopropyl-ether ethyl acetate), N-(1-benzyl-4-hydroxymethyl piperidine- 4-yl)-6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide 720 mg was obtained as a colorless crystal.

The example 14 of manufacture

6-(3,4-dimethoxyphenyl)-N-(4-phenyl piperidine- 4-yl) pyridine- 2-carboxamide 0.18 g The inside of DMF 3.5 ml, Cesium carbonate The bottom of existence of 140 mg, acetic acid (2-chloromethyl) It was made to react to phenyl 70 mg at a room temperature for 20 hours. They are inside of THF 10 ml, and 1M sodium hydroxide solution about the rough product obtained by carrying out post-processing with a conventional method. It was made to react to 3 ml at room temperature -50 ** for 16.5 hours. After making reaction mixture into neutrality with 1M hydrochloric acid aqueous solution, pH was set to about 8 in sodium bicarbonate solution, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Silica gel column chromatography (hexane-ethyl acetate) refines residue, and also it recrystallizes (ethanol diethylether), 6-(3,4-dimethoxyphenyl)-N-[1-(2-hydroxybenzyl)-4-phenyl-4-piperidyl] pyridine-2-carboxamide Monohydrate 85 mg was obtained as a colorless crystal.

[0073]

The example 15 of manufacture

6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid CDI 373mg was added to the THF 10 ml solution of 500 mg, and it stirred at the oil bath temperature of 60 ** for 1 hour. They are O-benzylhydroxylamine hydrochloride 367 mg and triethylamine to reaction mixture. 0.32 ml was added and it stirred at the oil bath temperature of 60 ** for 3 hours. Water was added to reaction mixture and ethyl acetate extracted. The saturation salt solution washed the organic layer, it dried with anhydrous magnesium sulfate, and the solvent was distilled off. Silica gel column chromatography (hexane-ethyl acetate) refines residue, and also it recrystallizes [diisopropyl ether / ethyl acetate], and is N-benzyloxy 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide. 566 mg was obtained as a colorless crystal.

The example 16 of manufacture

N-benzyloxy 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxamide Benzene of 400 mg To 10 ml solution, it is 10% palladium carbon. 50 mg and cyclohexene 5 ml was added and it stirred at the oil bath temperature of 80 ** for 4 hours. It is ethanol about the residue produced by filtering out an insoluble matter and distilling off a solvent. It dissolves in 10 ml and is 10% palladium carbon. 40 mg and ammonium formate 150 mg was added and it stirred at the oil bath temperature of 70 ** for 2 hours. The insoluble matter was filtered out, ethyl acetate was added to the residue produced by distilling off a solvent, and 1M sodium hydroxide solution extracted. 1M hydrochloric acid aqueous solution adjusted the water layer to pH 4, and chloroform extracted. The saturation salt solution washed the organic layer, it dried with anhydrous magnesium sulfate, and the solvent was distilled off. The obtained residue is ******ed from acetonitrile and it is 6-(3,4-dimethoxyphenyl)-N-hydroxypyridine- 2-carboxamide. 108 mg was obtained as a fine blackish brown crystal.

[0074]

The example 17 of manufacture

Bottom of ice-cooling m-chloroperbenzoic acid 400 mg was added to the dichloromethane 10 ml solution of 6-(3,4-dimethoxyphenyl)-N-[phenyl(pyridin-4-yl) methyl] pyridine- 2-carboxamide 1.00 g, and it stirred under ice-cooling for 30 minutes. m-chloroperbenzoic acid 400 mg was added and it stirred for 30 minutes. After adding m-chloroperbenzoic acid 400 mg, to the room temperature, temperature up was carried out and it stirred for 30 minutes. Water was added to reaction mixture, chloroform extracted, and water, saturated sodium subsulfite solution, and a saturation salt solution washed the organic layer. The after-desiccation solvent was distilled off

for the organic layer with anhydrous magnesium sulfate. Silica gel column chromatography (chloroform methanol) refines residue, and it ranks second, It recrystallized [ethyl acetate / acetonitrile] and 6-(3,4-dimethoxyphenyl)-N-[phenyl(pyridin-4-yl) methyl] pyridine- 2-carboxamide 1.25 g was obtained as a colorless crystal.
The example 18 of manufacture
{N-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-N-(1,2,3,4-tetrahydronaphthalene 1-yl) amino} methyl acetate Methanol of 620 mg In 10 ml solution. 1M sodium hydroxide solution 3 ml and THF 10 ml were added, and it stirred at the room temperature for 16 hours. It is 1M hydrochloric acid aqueous solution to reaction mixture. 3 ml was added and the solvent was distilled off. Recrystallization is performed for the rough crystal obtained by washing residue with water from ethanol, and it is {N-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-N-(1,2,3,4-tetrahydronaphthalene 1-yl) amino} acetic acid. 472 mg was obtained as a colorless crystal.
[0075]
The example 19 of manufacture
cyclopentanone Acetic acid of 0.50 ml 5 ml solution -- 2-methoxy ethylamine 0.32 ml and hydrogenation -- doria -- SETOKISHIHOU -- base -- sodium 1.20 g was added and it stirred for 30 minutes at the room temperature. Toluene was added to reaction mixture, 1M sodium hydroxide solution was added to the residue obtained by distilling off a solvent, and ethyl acetate extracted. The saturation salt solution washed the organic layer and it dried with anhydrous magnesium sulfate. Crude N-(2-methoxy ethyl) cyclopentyl amine produced by distilling off a solvent, and 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid Using 400 mg, by the same method as the example 5 of manufacture. N-cyclopentyl 6-(3,4-dimethoxyphenyl)-N-(2-methoxy ethyl) pyridine- 2-carboxamide 215 mg was obtained as a colorless oily matter.
The example 20 of manufacture
2-chloro-6-(4-t-butoxycarbo NIRUPI perazine 1-yl) pyrazine 0.71 g was stirred for 7 hours among 4M chloride-ethyl acetate solution 15 ml and under the room temperature. The solvent was distilled off and the rough product of the 2-chloro-6-(piperazine 1-yl) pyrazine hydrochloride was obtained. The rough product and 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid 0.62 g which were obtained by the same method as the example 5 of manufacture. 2-chloro-6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyrazine 594 mg was obtained as a light yellow crystal.
[0076]
The example 21 of manufacture
m-chloroperbenzoic acid 195 mg was added to the dichloromethane 10 ml solution of 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-(pyridin-4-yl) piperazine 353 mg, and it stirred at 5 ** for 1 hour. Sodium subsulfite solution was added to reaction mixture, and chloroform extracted. Water and a saturation salt solution washed the organic layer, it ranked second and the solvent was distilled off after desiccation with magnesium sulfate. Silica gel column chromatography (chloroform methanol) refines residue, and, subsequently it is recrystallized (ethanol ethyl acetate), 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-(1-oxide pyridin-4-yl) piperazine 1.5 hydrates 294 mg was obtained as a light yellow crystal.
The example 22 of manufacture
It is ammonium chloride to ethanol 70 ml of 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-(4-nitrophenyl) piperazine 2.5 g, and a water 25 ml mixed solution. 0.15 g and reduced iron 3.1 g was added and heating flowing back was carried out for 2 hours. Reaction mixture was filtered using cerite, saturated sodium bicarbonate solution was added to the residue obtained by carrying out vacuum concentration of the filtrate, and chloroform extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous

sodium sulfate. Silica gel column chromatography (chloroform methanol) refines residue, It is made to crystallize from acetonitrile ethyl acetate, and is a 1-[6-(3,4-dimethoxyphenyl) pyridine-2-carbonyl]-4-(4-aminophenyl) piperazine. 2.1 g was obtained as a light pink crystal.
[0077]
The example 23 of manufacture
1.6 M n-butyl lithium / n-hexane solution 1.75 ml was added to the THF 10 ml solution of 6-bromo-2,3-dihydro-1,4-benzodioxine 500 mg at -78 **. -After stirring at 78 ** for 1 hour, it stirred for 15 hours, having added trimethyl borate 0.78 ml and carrying out temperature up to a room temperature gradually. Distill off the solvent of reaction mixture and residue is dissolved in dimethoxyethane 10 ml, Ethanol 2 ml, N-(Indang 1-yl)-6-bromopyridine- 2-carboxamide 500 mg, Palladium acetate (II) 30 mg, triphenyl phosphine 150 mg and sodium carbonate Water of 335 mg 2 ml solution was added and heating flowing back was carried out for 5 hours. Ethyl acetate was added to the residue produced by distilling off a solvent after filtering out an insoluble matter, and the solvent was distilled off after washing with saturated sodium bicarbonate water and a saturation salt solution. Silica gel column chromatography (hexane-ethyl acetate) refines residue, and also it recrystallizes [diisopropyl ether / ethyl acetate], 6-(2,3-dihydro-1,4-benzodioxine 6-yl)-N-(Indang 1-yl) pyridine- 2-carboxamide 320 mg was obtained as a colorless crystal.
The example 24 of manufacture
6-(4-hydroxy-3-methoxypheny)-N-Indang 1-yl pyridine- 2-carboxamide In the DMF 5 ml solution of 320 mg. The bottom of ice-cooling, dimethylamine hydrochloride (2-chloroethyl) 200 mg and 60% sodium hydride 91 mg was added and it stirred for 1.5 days at the oil bath temperature of 80 **. Water was added to the residue obtained by distilling off a solvent, and ethyl acetate extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Silica gel column chromatography (chloroform - chloroform methanol) refines residue, and it is a blackish brown oily matter. 106 mg was obtained. It is ethanol about this compound. It dissolves in 2 ml and is fumaric acid. It recrystallizes [ethyl acetate / ethanol], after adding 28 mg and considering it as fumaric acid chloride, 6--[[4-(2-dimethylamino ethoxy)-3-methoxypheny]] N-Indang 1-yl pyridine- 2-carboxamide 1 fumaric acid chloride 104 mg was obtained as a colorless crystal.
[0078]
The example 25 of manufacture
6-(4-hydroxy-3-methoxypheny)-N-Indang 1-yl pyridine- 2-carboxamide 2-butanone of 310 mg In 10 ml solution. 3-chloromethyl pyridinehydrochloride 170 mg and potassium carbonate 276 mg were added, and it stirred at the oil bath temperature of 60 ** for 13 hours, and also stirred for one day at the oil bath temperature of 80 **. Water was added to the residue obtained by distilling off the solvent of reaction mixture, and ethyl acetate extracted. The saturation salt solution washed the organic layer, it dried with anhydrous magnesium sulfate, and the solvent was distilled off. Silica gel column chromatography (hexane-ethyl acetate - chloroform methanol) refines residue, and also it recrystallizes [diisopropyl ether / ethyl acetate], N-Indang 1-yl- 6-[3-methoxy-4-(pyridin-3-ylmethoxy) phenyl] pyridine- 2-carboxamide 110 mg was obtained as a colorless crystal.
The example 26 of manufacture
It is ethyl bromoacetate to THF 10 ml of 6-(3-hydroxy-4-methoxypheny)-N-(Indang 1-yl) pyridine- 2-carboxamide 360 mg, and a DMF 10 ml solution. 120 mg and potassium carbonate 690 mg is added, It stirred at 50 ** for 5 hours. After distilling off a solvent, water was added and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the after-desiccation solvent was distilled off with magnesium sulfate. It is 1M sodium hydroxide solution to the ethanol 10 ml solution of the obtained rough product. 7 ml was added and it was

made to react at a room temperature for 2 hours. 1M hydrochloric acid aqueous solution was added to reaction mixture, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Residue is ******ed from ethyl acetate diethylether and it is {5-[6-(Indang 1-yl carbamoyl) pyridin-2-yl]-2-methoxy phenoxy} acetic acid. 245 mg was obtained as a colorless crystal.

[0079]

The example 27 of manufacture

6-(3-hydroxy-4-methoxypheny)-N-(Indang 1-yl) pyridine- 2-carboxamide It is a chloridation 2-dimethylaminoethyl hydrochloride to THF 10ml of 360 mg, and a DMF 10 ml solution. 144 mg and potassium carbonate 690 mg. In addition, it stirred at 50 ** for 5 hours. After distilling off a solvent, water was added and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. After crystallizing residue by diethylether, it recrystallizes [diethylether / ethanol], and it is 6-[3-(2-dimethoxy aminoethoxy)-4-methoxypheny]-N-(Indang 1-yl) pyridine- 2-carboxamide. 110 mg was obtained as a colorless crystal.

The example 28 of manufacture

6-(3-amino-4-methoxypheny)-N-Indang 1-yl pyridine- 2-carboxamide 1.00 g of pyridine To 15 ml solution, they are the bottom of ice-cooling, and an acetyl chloride. Methylene chloride of 0.22 ml 5 ml solution was added. The solvent was distilled off after 1.5-hour stirring at the room temperature, water was added to residue, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Residue is ******ed from ethanol and it is 6-(3-acetylamino 4-methoxypheny)-N-Indang 1-yl pyridine- 2-carboxamide. 829 mg was obtained as a colorless crystal.

[0080]

The example 29 of manufacture

6-(3-ethyl-4-vinylphenyl)-N-Indang 1-yl pyridine- 2-carboxamide Ethanol of 205 mg To 5 ml solution, it is 10% palladium carbon. 30 mg was added and it stirred at the room temperature under the hydrogen atmosphere of ordinary pressure for 17 hours. An insoluble matter is filtered out, silica gel column chromatography (hexane-ethyl acetate) refines the residue which might be distilled off in the solvent, and it is 6-(3,4-diethylphenyl)-N-Indang 1-yl pyridine- 2-carboxamide. 186 mg was obtained as a colorless oily matter.

The example 30 of manufacture

6-(3-amino-4-methoxypheny)-N-Indang 1-yl pyridine- 2-carboxamide 0.75 g of ethanol To 10 ml solution, it is 1H-benzotriazol 1-methanol. 312 mg was added and it stirred under the room temperature for 19 hours. Separate the depositing yellow solid, THF 5 ml is made suspended, and it is sodium borohydride. 74 mg was added. Saturated sodium bicarbonate solution was violently added after stirring under the room temperature for 1.5 hours, and chloroform extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. In ethanol the compound obtained by silica gel column chromatography (hexane-ethyl acetate) refining residue as an oxalate, N-Indang 1-yl- 6-(4-methoxy-3-methylamino phenyl) pyridine- 2-carboxamide 1 oxalate monohydrate 30 mg was obtained as a colorless crystal.

[0081]

The example 31 of manufacture

6-(4-methoxy-3-nitrophenyl)-N-Indang 1-yl pyridine- 2-carboxamide 0.37-g THF 5 ml and methanol To 5 ml solution, it is 10% palladium carbon. 0.40 g was added and it stirred in a hydrogen atmosphere. 65 After hydrogen consumption of ml, 37% formaldehyde solution 1.96

ml and acetic acid 3 ml was added and it stirred at the bottom room temperature of a hydrogen atmosphere. Cerite filtration of the reaction mixture was carried out, sodium bicarbonate solution was added to filtrate, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Add 4M hydrogen chloride / ethyl acetate solution to residue, and heat diisopropyl ether washes the residue produced by distilling off a solvent, 6-(4-methoxy-3-dimethylaminophenyl)-N-Indang 1-yl pyridine- 2-carboxamide A little salt acid chloride Dihydrate 101 mg was obtained as a light brown crystal.

The example 32 of manufacture

1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine A little salt acid chloride Ethanol of 327 mg To 6 ml solution, it is triethylamine. 0.28 ml and 2,4-dichloropyrimidine 148 mg was added and it stirred at the oil bath temperature of 90 ** for 2 hours. After distilling off a solvent, water was added and chloroform extracted. The organic layer was washed with water and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. Silica gel column chromatography (hexane-ethyl acetate) refines residue, and also it recrystallizes [diisopropyl ether / acetonitrile], 2-chloro-4- {4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyrimidine Monohydrate 70 mg was obtained as a colorless crystal.

[0082]

The example 33 of manufacture

4- {4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} benzoic acid CDI 63 mg was added to the THF 5 ml solution of 171 mg, and it stirred at 60 **. Furthermore, CDI 52 mg was stirred at 60 ** [times / 2] for a total of 24 hours. They are after cooling and an ammonia solution to a room temperature about reaction mixture. 0.25 ml is added, and it stirs at a room temperature for 6 hours, and also is an ammonia solution. 0.5 ml was added and it stirred at the room temperature. The precipitated rough crystal was separated, it recrystallized [methanol / THF], and 4- {4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} BENZAMIDO 68 mg was obtained as a colorless crystal.

The example 34 of manufacture

4-(4- {4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenylcarbamoyl) piperidine- 1-carboxylic acid Benzyl Ethanol of 159 mg To the mixed solution of 8 ml and THF 8 ml, under argon atmosphere, Palladium carbon 18 mg was added 10%. It filtered after stirring under an ordinary pressure hydrogen atmosphere for 2 hours using cerite at the room temperature, and vacuum concentration of the filtrate was carried out. Silica gel column chromatography (chloroform methanol ammonia solution) refines residue, and it crystallizes from acetonitrile, 4'- {4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} piperidine- 4-carboxyanilide 70 mg was obtained as a colorless crystal.

[0083]

The example 35 of manufacture

Trifluoroacetic acid 5 ml was added to 5 ml of chloroform solution of 1-(benzofuran-5-yl)-4-(t-butoxycarbonyl) piperazine 1.20 g at 0 **, and it stirred for 1 hour, after carrying out temperature up to a room temperature. 1 After M sodium hydroxide solution neutralized, chloroform extracted. The saturation salt solution washed the organic layer. It is made below to be the same as that of the example 5 of manufacture after desiccation using 500 mg among 1-(benzofuran-5-yl) piperazine 910 mg produced by distilling off a solvent with anhydrous magnesium sulfate, 1-(benzofuran-5-yl)-4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 420 mg was obtained as a colorless crystal.

The example 36 of manufacture

In the DMF 3 ml solution of 1-(4-aminophenyl)-4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 355 mg. 1-chloro-2-(2-chloroethoxy) ethane 130 mg, sodium iodide 77 mg

and potassium carbonate 249 mg was added and it stirred at 100 ** overnight. The reaction solution was condensed under decompression after cooling to the room temperature, water was added, and chloroform extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous sodium sulfate. Silica gel column chromatography (chloroform methanol) refines residue, and it crystallizes from ethanol diethylether, 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine 210 mg was obtained as a yellow crystal.

[0084]

The example 37 of manufacture

To the THF 2.5 ml solution of 1-(4-aminophenyl)-4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 211 mg, it is methanesulfonyl chloride. 63.5 mg and triethylamine 76.8 mul were added, and it stirred overnight [bottom of room temperature]. Methanesulfonyl chloride 79 mg and triethylamine 103 mul was stirred at the room temperature [times / 2] for 3 hours. Water was added to reaction mixture and ethyl acetate extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous sodium sulfate. Silica gel column chromatography (chloroform methanol) refines residue, and it crystallizes from ethyl acetate diisopropyl ether, 4'-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} methanesulfon anilide 175 mg was obtained as a light purple crystal.

The example 38 of manufacture

[(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} benzoyl) amino] ethyl acetate Concentrated-hydrochloric-acid 0.8 ml was added to 233 mg, and it stirred overnight [bottom of room temperature]. Reaction mixture was crystallized from 2-propano rouge isopropyl ether after concentration under decompression, and [(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} benzoyl) amino] acetate acid chloride was separated. Filtrate is condensed under decompression, residue is crystallized from hexane, and it is [(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} benzoyl) amino] acetic acid. 1 hydrate 88 mg was obtained as a light blackish brown crystal.

[0085]

The example 39 of manufacture

1-(t-butoxycarbonyl) piperazine 2.00 g and potassium carbonate 2.00 g were added to the NMP 7.5 ml solution of 2,5-dichloro pyrazine 1.51 g, and heating stirring was carried out at 100 ** for 1 hour. It cooled to the room temperature, water was added, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and the after-desiccation solvent was distilled off with anhydrous magnesium sulfate. Silica gel column chromatography (chloroform methanol) refined residue, and the 2-chloro-5-(4-t-butoxycarbo NIRUPI perazine 1-yl) pyrazine of 2.73 g was obtained. 2-chloro-5-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyrazine was obtained as a colorless crystal like the example 35 of manufacture below using this.

The example 40 of manufacture

2-chloro-4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyrimidine One hydrate Methanol of 460 mg In 20 ml solution. 10% palladium carbon 150 mg was added and it stirred at the room temperature under an ordinary pressure hydrogen atmosphere for 23 hours. Filter out an insoluble matter, and silica gel column chromatography (chloroform methanol) refines the residue which might be distilled off in the solvent, and also it recrystallizes [diisopropyl ether / acetonitrile], 4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyrimidine 83 mg was obtained as a colorless crystal.

[0086]

The example 41 of manufacture

4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-1-(4-hydroxyphenyl) piperazine To 297 mg, it

is the [1,3] dioxolane 2. - One 623 mg and potassium carbonate 147 mg were added, and it half[1 hour and]-stirred at 100 **. Water was added after cooling and to reaction mixture to the room temperature, and 1M chloride was added to the pan. Saturated sodium bicarbonate solution neutralized and chloroform extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous sodium sulfate. Silica gel column chromatography (chloroform methanol) refines residue, and it recrystallizes [ethyl acetate], 2-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) ethanol 41 mg was obtained as a light yellow crystal.

The example 42 of manufacture

6-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} pyridin-3-oar In the DMF 5 ml solution of 213 mg. The bottom of ice-cooling, dimethylamine (2-chloroethyl) Hydrochloride 81 mg and 60% sodium hydride 43 mg was added. After 1-hour stirring and water were added at the oil bath temperature of 70 **, and ethyl acetate extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous sodium sulfate. The output (110 mg) which refined and obtained residue with silica gel column chromatography (chloroform - chloroform methanol) is dissolved in ethanol, Oxalic acid It recrystallizes [ethanol], after adding 40 mg and considering it as an oxalate, A 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-[5-(2-dimethylamino ethoxy)-2-pyridyl] piperazine 2 oxalate 81 mg was obtained as a colorless crystal.

[0087]

The example 43 of manufacture

4-[2-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenoxy) ethyl] piperazine 1-carboxylic acid t-butyl Chloroform of 270 mg 3 ml solution -- 4M hydrogen chloride / ethyl acetate solution . 0.427 ml was added and it stirred at the room temperature for two days. Furthermore, they are chloroform 2 ml, and 4M hydrogen chloride / ethyl acetate solution. 1 ml was added and it stirred at the room temperature overnight. Add ethanol to reaction mixture, separate a rough crystal, and it recrystallizes [methanol], 1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-[4-(2-piperazine 1-yl ethoxy) phenyl] piperazine Four hydrochlorides 3 hydrate 114 mg was obtained as a light yellow crystal.

The example 44 of manufacture

(**)-trans-1-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-2,5-dimethyl 4-(4-nitrophenyl) piperazine ethanol 37 ml of 1.42 g, and a water 13 ml mixed solution -- ammonium chloride . 0.16 g and reduced iron 1.66 g was added and heating flowing back was carried out for 0.5 hour. Reaction mixture was filtered using cerite, saturated sodium bicarbonate solution was added to the residue obtained by carrying out vacuum concentration of the filtrate, and chloroform extracted. The saturation salt solution washed the organic layer and the solvent was distilled off after desiccation with anhydrous magnesium sulfate. The compound obtained by silica gel column chromatography (chloroform methanol) refining residue was processed with 4M hydrogen chloride / ethyl acetate solution, and the solvent was distilled off after salt formation. ethyl acetate washes residue -- (**)-trans-4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-2,5-dimethylpiperazine 1-yl} aniline Two hydrochlorides Two hydrates 582 mg was obtained as a light yellow crystal.

The examples 45-217 of manufacture

The compound of the examples 45-217 of manufacture shown in the after-mentioned tables 1-17 was obtained like the method of the above-mentioned example of manufacture, respectively. The structure and physicochemical data of a compound of the examples 1-217 of manufacture are shown in Tables 1-17.

[0088]

Example 5 (manufacture of alpha type crystal of compound A)

Crude 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine (compound A) Ethyl acetate 60 ml was added to 5.0 g, and it heated and dissolved to near flowing-back temperature under stirring. Subsequently, activated carbon 1.0 g was added, and also it filtered after stirring. Residue was washed by ethyl acetate 5 ml. After dissolving the crystal which heated filtrate and deposited, it cooled radiationally and stirred at 30 ** all night, and also it cooled and stirred at 0 ** for 4 hours. Reduced pressure drying of the precipitated crystal was separated and carried out, and alpha type crystal 3.97 g was obtained.

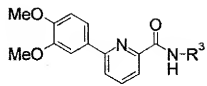
Example 6 (manufacture of beta type crystal of compound A)

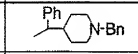
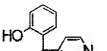
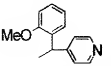
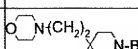
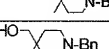
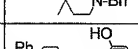
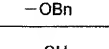
Crude compound A Methanol 13 ml and acetone 8 ml were added to 2.5 g, and it heated and dissolved to near flowing-back temperature under stirring. Subsequently, activated carbon 0.5 g was added, and also it filtered after stirring. Residue was washed by methanol 3 ml. A little alpha type crystals were added as seed crystal after dissolving the crystal which heated filtrate and deposited, stirring. Under stirring, it cooled gradually and the crystal which stirred all night and deposited at 0 ** was separated, with methanol, after washing, reduced pressure drying was carried out and crystal mixture 1.95 g of alpha type crystal and beta type crystal was obtained. Using 1.0 g of the obtained crystal mixture, methanol 5 ml and acetone 2 ml were added, and, subsequently it stirred at 12 hours and also 1 ** at 20 ** by 45 ** for 12 hours for 12 hours. The crystal was separated, with methanol, after washing, reduced pressure drying was carried out and beta type crystal 0.9 g was obtained.

Example 7 (manufacture of beta type crystal of compound A)

Compound A Ethanol 2680 ml and ethyl acetate 980 ml were added to 380.10 g. It heated and dissolved to near flowing-back temperature under stirring, and filtered at the time of heat. The filter paper and the filter were washed by ethyl acetate 100 ml, and were set by previous filtrate. A little beta type crystals were added as seed crystal after dissolving the crystal which heated filtrate and deposited, stirring at 65-70 **. It stirred at 40 ** after cooling gradually all night, and stirred at 0 ** after cooling further gradually all night. The precipitated crystal was separated, by ethanol, after washing, reduced pressure drying was carried out and beta type crystal 359.85 g was obtained.

[Table 1]



Ex	Syn	R^3	Dat	Sal
4	4		NMR1: 13.41 (1H, s), 5.06 (1H, dd, J= 9.3, 7.4Hz), 3.99 (3H, s); MP: 159-161	
5	5		NMR1: 8.58 (2H, d, J=4.3 Hz), 8.11 (1H, dd, J=7.8, 1.0Hz), 3.95 (3H, s) MP: 184-187	
6	6	$-C(Ph)_2CO_2H$	NMR2: 8.03(1H,t, J=7.8 Hz), 7.12 (1H, d, J=8.4 Hz), 3.94 (3H, s); MP: 209-212	
7	7		NMR2: 10.05 (1H, s), 6.44 (1H, q, J= 9.2 Hz), 3.88 (3H, s), 3.85 (3H, s); MP: 131-133	
8	8		NMR2: 6.72 (1H, d, J= 8.8 Hz), 3.88 (3H, s), 3.84 (3H, s), 3.83 (3H, s); MP: 172-174	HCl
9	9		NMR2: 8.20 (1H, d, J=7.8 Hz), 3.91 (3H, s), 2.23-2.17 (2H,m); MP: 195-203	Fum 1.5 H_2O
10	10		NMR2: 8.19 (1H, d, J=8.3Hz), 3.92 (3H, s), 2.43(3H,s); MP: 197-201	Fum
11	11		NMR2: 7.91 (1H, d, J=7.3 Hz), 4.13 (2H, s), 3.91 (3H, s); MP: 170-172	Ox
12	12		NMR2: 8.04 (1H, t, J=7.8 Hz), 3.89 (3H, s), 2.76 (2H, m); MP: 112-116	2 Fum H_2O
13	13		NMR1: 3.99 (3H, s), 3.84 (2H, d, J= 5.8Hz), 3.52 (2H,s); MP: 120-122	
14	14		NMR2: 8.79 (1H, s), 3.90 (3H, s), 3.85 (3H, s), 3.64 (2H, s); MP: 191-192	H_2O
15	15	$-OBn$	NMR1: 7.81 (1H, dd, J=7.8, 1.0 Hz), 5.10 (2H, s), 3.94 (3H, s); MP: 111-112	
16	16	$-OH$	NMR2: 7.99(1H, t, J=7.8Hz), 7.05 (1H, d, J=8.3 Hz), 3.91 (3H, s); MP: 170-173	
17	17		NMR1: 8.11 (1H, dd, J=7.8, 1.0 Hz), 6.34 (1H, d, J=7.3Hz), 3.95 (3H, s) MP:176-179	

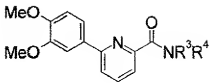
[0089]
[Table 2]

45	2		NMR1: 7.39 (1H, d, J=7.4 Hz), 5.70 (1H, dd, J=16.1 Hz, 7.8 Hz), 3.90 (3H, s); MP: 120-122	
46	2		NMR1: 7.52 (1H, s), 4.47 (2H, s), 3.34 (3H, s); MP: 146-148	
47	2		NMR2: 8.18 (1H, d, J=7.8Hz), 3.93 (3H, s), 3.60-3.51(4H,m); MP: 163-166	Fum MeCN
48	2		NMR1: 7.61 (1H, dd, J=8.3, 2.0 Hz), 3.99 (3H, s), 3.53 (2H, s); MP: 177-179	
49	2		F:407	
50	18		NMR2: 8.05 (1H, t, J=7.8Hz), 570 (1H, d, J=8.3Hz), 3.91 (3H, s); MP: 224-226	
51	2		F: 483	
52	18		NMR2: 12.93 (1H, s), 6.46(1H, d, J=8.8Hz), 3.88 (3H, s); MP: 208-209	
53	5		F:421	
54	18		NMR2: 8.03 (1H, t, J=7.8 Hz), 3.93 (3H, s), 3.07 (1H, dd, J=16.1, 6.9 Hz); MP: 181-182	
55	5		NMR2: 5.61 (1H,d,J=7.8Hz), 3.92 (3H, s), 2.36 (6H,s); MP: 185-187	1.5 Fum
56	5		NMR2: 8.16 (1H,d,J=7.8Hz), 3.83 (6H, s), 2.28 (3H,s); MP: 206-209	2 Fum
57	5		NMR2: 8.17 (1H,d,J=7.3Hz), 4.31-4.27 (2H,m) 3.84 (6H, s); MP: 141-142	Ox
58	5		NMR2: 6.46 (1H, d, J= 8.8 Hz), 3.89 (3H, s), 3.83 (3H, s); MP: 138-139	
59	5		NMR2: 7.12 (1H, d, J= 8.3 Hz), 6.63 (1H, d, J= 7.6 Hz), 3.94 (3H, s), 3.85 (3H, s); MP: 125-126	
60	5		F: 532	

[0090]
[Table 3]

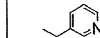
61	5		NMR1: 8.10 (1H, d, J=7.9 Hz), 4.00 (3H, s), 3.06 (1H, m); MP: 112-113	
62	2		NMR1: 7.02 (1H, d, J=8.4 Hz), 4.00 (3H, s), 3.51 (2H, s)	
63	18		NMR2: 12.52 (1H,s),7.35-7.23 (5H, m), 3.93 (3H, s); MP: 237-240	
64	5		NMR1: 4.03 (3H, s), 3.70-3.68 (4H, m), 2.16-2.12 (2H,m); MP: 212-214	
65	5		NMR2: 7.85 (1H, dd, J=7.3,1.9 Hz), 4.28(2H,d,J=5.4Hz), 3.91 (3H, s); MP:170-173	Ox
66	5		NMR1: 7.92 (1H, d, J=2.0 Hz), 6.36 (1H, d, J=7.3Hz), 4.13 (3H, s); MP: 167-169	
67	25		NMR1: 7.03 (1H, d, J=8.3Hz), 3.99 (3H, s), 3.54 (2H,s); MP: 189-190	
68	10		NMR1: 8.02 (1H, dd, J=6.8, 1.9 Hz), 4.00 (3H, s), 2.14 (2H, d, J=6.9Hz); MP: 148-150	
69	1		NMR2: 8.02 (1H, m), 5.20 (1H, td, J= 8.8, 5.4 Hz), 3.93 (3H, s); MP: 169-171	Ox
70	5		NMR1: 6.98 (1H,d,J=8.8Hz), 6.40 (1H,d,J=7.9Hz), 3.95 (3H,s,); MP: 144-146	

[0091]
[Table 4]

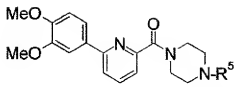


Ex	Syn	R^3	R^4	Dat	Sal
18	18		$-CH_2CO_2H$	F: 447 MP: 187-188	
19	19	$-(CH_2)_2OMe$		NMR1: 7.85 (1H, t, J=7.8 Hz), 3.94 (3H, s), 3.59 (2H, t, J=6.4 Hz); F: 385	

[0092]
[Table 5]

71	19		−iBu	NMR2: 3.83 (3H, s), 3.06-2.98 (3H,m) 0.72 (3H,d, J= 6.8Hz); MP: 187-192	Ox
72	19			F: 468 MP: 164-166	Ox
73	19			F: 531 MP: 137-138	
74	2		$-CH_2CO_2Me$	F: 461	
75	2			NMR2(120℃): 7.50 (1H,dd, J= 6.3, 1.0Hz), 5.40(1H,m), 3.82 (3H, s); MP: 125-127	
76	19			F: 481; MP: 139-141	
77	19			F: 530; MP: 148-150	
78	21			F: 496; MP: 153-154	
79	19			EI: 513; MP: 133-134	
80	19			F: 578; MP: 161-164	
81	19 & 18			F: 552; MP: 117-120	
82	5	$-(CH_2)_2OMe$		NMR1: 7.81 (1H, m), 3.95 (3H, s), 3.68-3.83 (2H, m); F: 431	
83	5			NMR2(120℃): 7.05 (1H, d, J= 8.0 Hz), 4.61 (1H, brs), 3.83 (6H, s); F: 531	
84	5			F:529 MP:149-153	Ox 1.5 H_2O

[0093]
[Table 6]



Ex	Syn	R^5	Dat	Sal
2	2	4-OMe-Ph	NMR1: 7.84 (1H, t, J=7.8 Hz), 3.96 (3H, s), 3.78 (2H, s); MP: 169-172	
3	3		NMR2: 3.85(3H,s), 3.82(3H, s), 3.13-3.16(4H,m), 2.79(6H,s); MP:136-137	2 Ox
20	20		NMR2: 8.32(1H, s), 7.90(1H, s), 3.88 (3H, s), 3.83 (3H, s); MP:160-161	
21	21	4-NH_2-Ph	NMR2: 8.28-8.30 (2H, m), 3.87 (3H, s), 3.83 (3H, s); F: 421	1.5 H_2O
22	22	4-Ac-Ph	NMR2: 4.62 (2H, br s), 3.85 (3H, s), 2.98-3.03 (4H, m); MP: 164-165	
32	32		NMR1: 8.10 (1H, d, J=6.3 Hz), 6.98 (1H, d, J=8.7 Hz), 6.43 (1H, d, J=6.3 Hz); MP: 98-100	H_2O
33	33	4-$CONH_2$-Ph	NMR2: 3.85 (3H, s), 7.03 (1H, br s), 7.68-7.79 (5H, m); MP: 237-240	
34	34		NMR2: 1.44-1.54 (2H, m), 3.85 (3H, s), 9.59 (1H, s); MP: 217-219	
35	35		NMR1: 6.97 (1H,d,J=8.3Hz), 6.69-6.71 (1H,m), 3.20-3.30 (4H,m); MP: 176-178	
36	36		NMR2: 3.69-3.73 (6H, m), 3.85 (3H, s), 6.85-6.91 (4H, m); MP: 129-130	
37	37	4-($NHSO_2Me$)-Ph	NMR2: 2.88 (3H, s), 3.82 (3H, s), 9.28 (1H, s); MP: 168-170	
38	38		NMR2: 3.82 (3H, s), 8.55 (1H, t, J=5.8 Hz), 12.50 (1H, br s); MP: 114-117	H_2O
39	39		NMR1: 8.11 (1H,d,J=1.5Hz), 6.98 (1H,d,J=8.3Hz), 3.69-3.80 (4H,m); MP: 160-162	
40	40		NMR1: 8.63 (1H, s), 8.26 (1H, d, J=6.3 Hz), 6.98 (1H, d, J=8.3 Hz); MP: 138-139	

[0094]

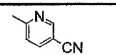
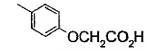
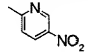
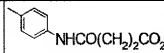
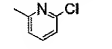
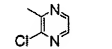
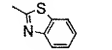
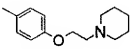
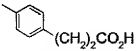
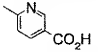
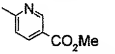
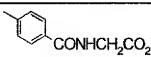
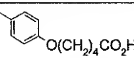
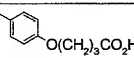
[Table 7]

41	41		NMR2: 3.65-3.72 (4H, m), 3.82 (3H, s), 4.80 (1H, t, J=5.4 Hz); MP: 111-113	
42	42		NMR1: 6.66 (1H, d, J=8.8 Hz), 3.97 (3H, s), 3.95 (3H, s), 2.91 (6H, s); MP: 144-147	2 Ox
43	43		NMR2: 3.82 (3H, s), 3.84 (3H, s), 7.68-7.72 (2H, m); MP: 155-158	4 HCl 3 H_2O
85	2	4-NMe_2-Ph	NMR1: 7.78(1H, dd, J= 8.3, 1.0 Hz), 3.96(3H, s), 2.53(3H,s); MP: 161-163	
86	5		NMR2: 3.85(3H,s), 3.82(3H,s), 3.05-3.08(4H,m), 2.79(6H,s); MP: 159-161	
87	5		NMR2: 8.36 (1H, d, J=0.9 Hz), 7.09 (1H, d, J= 8.0 Hz), 3.86 (3H, s), 3.82 (3H, s); MP: 122-124	
88	5		NMR2: 8.19 (2H, d, J= 5.9 Hz), 3.86 (3H, s), 3.82 (3H, s), 3.45-3.52 (4H, m); MP: 155-156	
89	5	2-Cl-4-OMe-Ph	NMR2: 7.15 (1H, d, J = 9.0 Hz), 7.05 (1H, d, J =3.0 Hz), 6.91 (1H, dd, J = 9.0, 3.0 Hz); MP: 155-156	
90	5	4-CN-Ph	NMR2: 8.06(1H,d,J=7.8Hz), 3.85 (3H,s), 3.47-3.54(4H,m); MP: 146-148	
91	5	4-CO_2Et-Ph	NMR2: 3.86(3H, s), 3.45-3.51(4H, m), 1.29(3H, t,J=7.3Hz); MP: 112-114	
92	10	-CH_2-(2-OH-3-OMe-Ph)	NMR1: 7.54 (1H,dd, J=8.3, 2.0 Hz), 3.78 (2H, s), 2.76-2.66 (4H,m); MP: 155-158	
93	10		NMR1: 6.97 (1H,d,J=8.3Hz), 3.98 (3H, s), 2.09 (3H, s); MP: 120-122	
94	5& 20		NMR2: 3.86 (3H, s), 3.83 (3H, s), 2.75 (3H, d, J= 4.4 Hz); F: 530	2 HCl 2 H_2O
95	5& 20		NMR2: 8.67 (1H, t, d= 5.4 Hz), 3.86 (3H, s), 3.83 (3H, s), 2.82 (3H, s), 2.80 (3H, s); F: 518	2 HCl 2 H_2O
96	3	4-NHAc-Ph	NMR2: 1.99 (3H, s), 3.85 (3H, s), 9.71 (1H, s); MP: 201-203	
97	3	4-(NHCO-Ph)-Ph	NMR2: 3.82 (3H, s), 6.98 (2H, d, J=9.3 Hz), 10.07 (1H, s); MP: 169-171	
98	37	4-($NHSO_2$-Ph)-Ph	NMR2: 3.82 (6H, s), 6.80-6.85 (2H, m), 9.85 (1H, s); MP: 187-189	

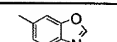
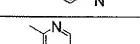
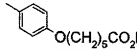
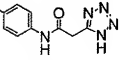
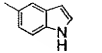
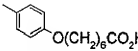
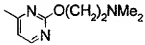
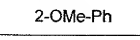
[0095]
[Table 8]

99	5		NMR2: 1.19 (6H, t, J=7.4 Hz), 2.72-2.75 (2H, m), 10.02 (1H, s); MP: 131-134	Ox
100	18	4-CO_2H-Ph	NMR2: 3.86 (3H, s), 6.99 (2H, d, J=9.3 Hz), 12.32 (1H, br s); MP: 209-211	
101	5	4-OH-Ph	NMR2: 3.84 (3H, s), 6.82 (2H, d, J=8.8 Hz), 8.88 (1H, s); MP: 177-179	
102	5	4-NO_2-Ph	NMR2: 3.86 (3H, s), 7.04 (2H, d, J=9.2 Hz), 8.06-8.10 (3H, m); MP: 142-144	
103	5		NMR1: 7.05 (1H, d, J=9.8 Hz), 6.98 (1H, d, J=8.3 Hz), 6.89 (1H, d, J=9.3 Hz), 4.04 (3H, s); MP: 171-172	
104	5		NMR1: 7.58 (1H, dd, J=8.3, 2.0 Hz), 6.98 (1H, d, J=8.3 Hz), 3.85 (3H, s), 3.40-3.28 (4H, m); MP: 158-159	
105	5		NMR1: 7.01 (1H,m), 6.98 (1H,d, J=8.3Hz), 3.56-3.61 (4H,m); MP: 141-143	
106	5	3-Cl-4-OMe-Ph	NMR1: 6.98 (1H,d,J=8.8Hz), 3.86 (3H,s), 3.13-3.24 (4H,m); MP: 158-159	
107	5		NMR1: 7.57 (1H, dd, J=8.3, 2.4 Hz), 6.94 (1H, d, J=9.7 Hz), 3.86-3.74 (4H, m); MP: 161	
108	5	4-Ac-3-CF_3-Ph	NMR2: 2.52 (3H, s), 3.82 (3H, s), 7.83 (1H, d, J=8.7 Hz); MP: 142-143	
109	5	3-F-4-OMe-Ph	NMR1: 6.97 (1H,d,J=8.3Hz), 3.85 (3H,s), 3.13-3.24 (4H,m); MP: 155-156	
110	5		NMR1: 6.97 (1H, d, J=8.7 Hz), 6.71 (1H, d, J=8.8Hz), 3.90 (3H, s), 3.24-3.11 (4H, m); MP: 179-181	
111	5		NMR1: 8.74 (1H, dd, J=4.4, 1.5 Hz), 3.97 (3H, s), 3.95 (3H, s), 3.50-3.38 (4H, m); MP: 144-145	
112	5		NMR2: 3.85 (3H, s), 4.03-4.21 (4H, m), 6.46-6.49 (2H, m); MP: 187-188	
113	5	4-SO_2NH_2-Ph	NMR2: 3.85 (3H, s), 7.05-7.10 (5H, m), 7.65 (2H, d, J=9.3 Hz); MP: 213-214	
114	3	4-Ac-3-OH-Ph	NMR2: 2.49 (3H, s), 3.86 (3H, s), 12.76 (1H, s); MP: 135-137	

[0096]
[Table 9]

115	5		NMR1: 8.43 (1H, d, J=1.9 Hz), 3.90 (3H, s), 3.87-3.82 (4H, m); MP: 162-163	
116	18		NMR2: 3.84 (3H, s), 4.58 (2H, s), 12.90 (1H, br s); MP: 143-145	H_2O
117	5		NMR1: 9.04 (1H, d, J=2.9 Hz), 6.98 (1H, d, J=8.3 Hz), 6.61 (1H, d, J=9.2 Hz); MP: 183-184	
118	3		NMR2: 2.56-2.59 (4H, m), 3.59 (3H, s), 9.78 (1H, s); MP: 140-142	
119	5		NMR1: 6.52 (1H, d, J=8.3 Hz), 3.99 (3H, s), 3.95 (3H, s), 3.75-3.68 (4H, m); MP: 107-109	
120	5		NMR1: 8.15 (1H,d,J=2.4Hz), 6.97 (1H,d,J=8.3Hz), 3.55-3.64 (4H,m); MP: 140-142	
121	5		NMR1: 7.09-7.13 (1H,m), 6.98 (1H,d, J=8.3Hz), 3.79-3.83 (4H,m); MP: 172-173	
122	27		NMR2: 1.71-1.76 (4H, m), 3.82 (3H, s), 4.26 (2H, t, J=4.9 Hz); MP: 161-165	1.5 Ox
123	35	2-Cl-4-Ac-Ph	NMR1: 7.04 (1H,d,J=8.3Hz), 6.97 (1H,d,J=8.3Hz), 2.56 (3H,s); MP: 164-165	
124	18		NMR2: 12.06 (1H,s), 7.53 (1H,d, J=7.4Hz), 2.73 (2H,t,J=7.6Hz); MP: 169-171	
125	18		NMR2: 12.56 (1H, br), 8.65 (1H, d, J=2.0 Hz), 7.09 (1H, d, J=8.3 Hz); MP: 220-222	
126	5		NMR1: 8.81 (1H, d, J=2.5 Hz), 3.98 (3H, s), 3.95 (3H, s), 3.88 (3H, s); MP: 157-159	
127	5		NMR2: 1.20 (3H, t, J=6.9 Hz), 3.82 (3H, s), 8.63-8.66 (1H, m); MP: 83-85	
128	18		NMR2: 1.59-1.73 (4H, m), 3.85 (3H, s), 12.02 (1H, s); MP: 79-81	H_2O
129	18		NMR2: 2.32-2.39 (2H, m), 3.85 (3H, s), 12.11 (1H, br s); MP: 123-125	

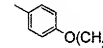
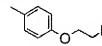
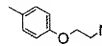
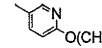
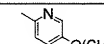
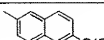
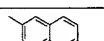
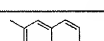
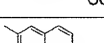
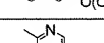
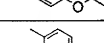
[0097]
[Table 10]

130	35		NMR1: 7.98 (1H,s), 6.98 (1H,d, J=8.3Hz), 3.28-3.41 (4H,m); MP: 151-153	
131	33		NMR2: 7.78 (1H, br), 7.16 (1H, br), 6.88 (1H, d, J=8.8 Hz), 3.87 (3H, s); MP: 243-244	
132	18		NMR2: 1.36-1.44 (2H, m), 3.85 (3H, s), 11.98 (1H, s); MP: 91-93	H_2O
133	3	4-CH_2OH-Ph	NMR2: 3.82 (3H, s), 4.39 (2H, d, J=5.9 Hz), 4.96 (1H, t, J=5.9 Hz); MP: 150-152	
134	5		NMR1: 8.41 (1H, s), 6.98 (1H, d, J=8.3 Hz), 3.98 (3H, s); MP: 119-120	
135	27	4-Ac-3-OMe-Ph	NMR2: 2.44 (3H, s), 3.88 (3H, s), 6.58 (1H, s); MP: 117-118	0.5 H_2O
136	5		NMR2: 4.09 (2H, S), 10.23 (1H, s), 16.22 (1H, br); MP: 217-219	0.5 H_2O
137	5		NMR1: 6.55 (1H, d, J=8.3 Hz), 4.00 (3H, s), 3.95 (3H, s), 3.75-3.66 (4H, m); MP: 144-145	
138	5		NMR1: 7.32 (1H, d, J=8.8 Hz), 3.96 (3H, s), 3.94 (3H, s), 3.31-3.18 (4H, m); MP: 193-194	
139	5		NMR1: 8.21 (1H, d, J=2.4 Hz), 3.98 (3H, s), 3.95 (3H, s), 3.70-3.64 (4H, m); MP: 127-128	
140	18		NMR2: 3.85 (3H, s), 9.75 (1H, s), 12.09 (1H, br); MP: 167-170	
141	18		NMR2: 1.28-1.43 (4H, m), 3.85 (3H, s), 11.97 (1H, br s); MP: 102-109	H_2O
142	5		NMR2: 4.53 (1H, t, J=4.9 Hz), 3.88 (3H, s), 3.83 (3H, s), 3.31-3.18 (4H, m), 2.81 (6H, s); MP: 180-181	1.5 Ox
143	5	2-OMe-Ph	NMR2: 3.79 (3H, s), 3.85 (3H, s), 6.87-7.02 (4H, m); MP: 162-163	
144	5	3-OMe-Ph	NMR2: 3.72 (3H, s), 3.85 (3H, s), 6.48-6.50 (1H, m); MP: 180-181	
145	18		NMR2: 1.91 (2H, quintet, J=6.8 Hz), 3.85 (3H, s), 12.12 (1H, br s); MP: 109-112	

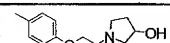
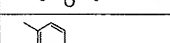
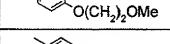
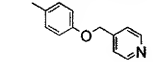
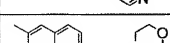
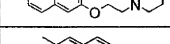
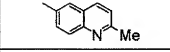
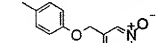
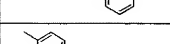
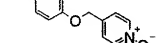
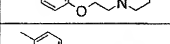
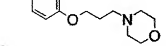
[0098]
[Table 11]

146	18		NMR2: 1.60-1.75 (4H, m), 3.85 (3H, s), 12.03 (1H, br); MP: 119-120	H_2O
147	18		NMR2: 1.37-1.45 (2H, m), 3.85 (3H, s), 11.98 (1H, s); MP: 97-99	
148	18		NMR2: 11.97 (1H,s), 7.52 (1H,d, J=7.4Hz), 2.22 (2H,t,J=6.9Hz); MP: 159-161	
149	18		NMR2: 6.13 (1H, d, J=7.3 Hz), 3.87 (3H, s), 3.83 (3H, s), 2.21 (1H, t, J=7.6 Hz); MP: 182-185	
150	18		NMR1: 7.93 (1H, d, J=2.9 Hz), 3.97 (3H, s), 3.94 (3H, s), 2.57 (1H, t, J=7.1 Hz); MP: 122-124	
151	27		NMR2: 1.22 (6H, t, J=7.3 Hz), 3.45-3.48 (2H, m), 3.82 (3H, s); MP: 97-99	Ox H_2O
152	18		NMR1: 6.97 (1H,d,J=8.8Hz), 6.63 (1H,d,J=8.8Hz), 2.61 (2H,t,J=7.3Hz); MP: 190-191	
153	18		NMR2: 1.97 (2H, quintet, J=6.8 Hz), 3.82 (3H, s), 12.11 (1H, s); MP: 133-134	
154	18		NMR2: 1.66-1.80 (4H, m), 3.82 (3H, s), 12.01 (1H, s); MP: 176-178	
155	18		NMR2: 1.42-1.50 (2H, m), 3.82 (3H, s), 12.11 (1H, br); MP: 129-130	
156	18		NMR1: 6.96 (1H,d,J=8.3Hz), 6.62 (1H,d,J=8.8Hz), 2.36 (2H,t,J=6.8Hz); MP: 158-160	
157	33	4-(CONHMe)-Ph	NMR2: 2.75 (3H, d, J=3.5 Hz), 3.85 (3H, s), 8.13-8.18 (1H, m); MP: 140-141	
158	18		NMR1: 7.14 (1H, d, J=8.8 Hz), 4.00 (3H, s), 3.95 (3H, s), 2.65 (1H, t, J=7.1 Hz); MP: 189-191	
159	36		NMR2: 1.45-1.52 (2H, m), 3.85 (3H, s), 6.83-6.88 (4H, m); MP: 135-137	0.5 H_2O

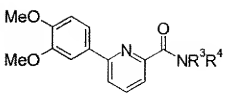
[0099]
[Table 12]

160	5	4-NEt_2-Ph	NMR2: 1.30 (6H, t, J=7.0 Hz), 3.23 (4H, q, J=7.0 Hz), 3.82 (3H, s); MP: 84-87	
161	33	4-($CONMe_2$)-Ph	NMR2: 2.95 (6H, s), 3.82 (3H, s), 7.32 (2H, d, J=8.3 Hz); MP: 81-83	H_2O
162	27		NMR2: 2.80 (6H, br s), 3.85 (3H, s), 6.85-6.95 (4H, m); F: 505	Ox H_2O
163	27		NMR2: 2.71 (3H, s), 3.82 (3H, s), 4.04 (2H, t, J=5.3 Hz); MP: 183 (dec)	Ox H_2O
164	27		NMR2: 1.33-1.42 (2H, m), 3.82 (3H, s), 4.52 (1H, d, J=3.9 Hz); MP: 143-144	
165	5		NMR2: 6.80 (1H, d, J=8.8 Hz), 3.85 (3H, s), 3.82 (3H, s), 2.78 (6H, s); MP: 114-115	Ox H_2O
166	42		NMR1: 3.97 (3H, s), 3.95 (3H, s), 3.59-3.54 (4H, m), 1.07 (6H, t, J=7.2 Hz); F: 520	HCl 2 H_2O
167	42		NMR2: 7.28 (1H, d, J=1.9 Hz), 3.87 (3H, s), 3.82 (3H, s), 2.80 (6H, s); MP: 195-198	Ox 0.5 H_2O
168	42		NMR2: 6.97 (1H, d, J=8.6 Hz), 4.71 (2H, s), 1.31 (3H, t, J=7.3 Hz); MP: 140-142	
169	18		NMR2: 4.74 (2H, s), 3.86 (3H, s), 3.82 (3H, s), 3.35-3.25 (4H, m); MP: 198-200	
170	18		NMR1: 6.97 (1H, d, J=8.3 Hz), 3.96 (3H, s), 3.94 (3H, s), 2.63 (2H, t, J=7.4 Hz); MP: 153-154	
171	42		NMR2: 7.35 (1H, dd, J=9.0, 3.4 Hz), 4.19 (2H, t, J=5.4 Hz), 2.78-2.76 (4H, m); MP: 163-165	Ox 0.5 H_2O
172	27		NMR2: 3.82 (3H, s), 5.09 (2H, s), 6.94 (4H, s); MP: 137-139	
173	27		NMR2: 1.12-1.23 (2H, m), 3.82 (3H, s), 6.90-6.97 (4H, m); MP: 202-205	Ox 0.5 H_2O

[0100]
[Table 13]

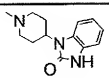
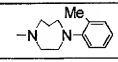
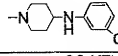
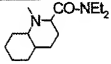
174	27		NMR2: 2.15 (1H, br), 3.82 (3H, s), 4.23 (2H, t, J=5.3 Hz), ; F: 533	2 Ox
175	27		NMR2: 3.30 (3H, s), 3.82 (3H, s), 4.00-4.02 (2H, m), ; MP: 104-108	
176	27		NMR2: 3.82 (3H, s), 5.12 (2H, s), 6.93 (4H, s); MP: 140-142	
177	42		NMR2: 7.37 (1H, dd, J=8.8, 2.4 Hz), 4.28 (2H, t, J=5.4 Hz), 3.85 (3H, s), 3.82 (3H, s); MP: 167-173	Ox 0.5 H_2O
178	18		NMR2: 8.76 (1H, d, J=8.8 Hz), 3.86 (3H, s), 3.83 (3H, s), 2.91 (3H, s); MP: 135-140	2 HCl 2 H_2O
179	27		NMR2: 5.06 (2H, s), 6.94 (4H, s), 8.28 (1H, br s); MP: 147-148	
180	27		NMR2: 3.82 (3H, s), 5.05 (2H, s), 8.19-8.23 (2H, m); MP: 182-183	
181	27		NMR2: 3.82 (3H, s), 4.13-4.16 (2H, m), 6.88-6.95 (4H, m); MP: 109-111	1.5 Ox
182	27		NMR2: 2.15-2.23 (2H, m), 3.82 (3H, s), 6.96-7.02 (2H, m); MP: 213-217	2 HCl 1.5 H_2O
183	27		NMR2: 3.28 (6H, s), 3.82 (3H, s), 4.16 (2H, t, J=5.4 Hz); F: 579	2 Ox
184	27		NMR2: 3.82 (3H, s), 4.00-4.05 (2H, m), 6.86 (2H, d, J=8.8 Hz); MP: 106-109	2 Ox 2 H_2O
185	18		NMR2: 1.93 (2H, t, J=6.9 Hz), 3.85 (3H, s), 5.51 (1H, br); MP: 165-170	3 HCl
186	18		NMR2: 2.79 (3H, br s), 3.85 (3H, s), 12.06 (1H, s); MP: 138-139	H_2O

[0101]
[Table 14]

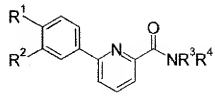


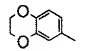
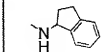
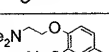
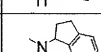
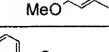
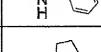
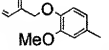
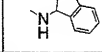
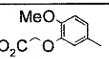
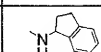
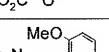
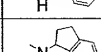
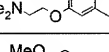
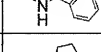
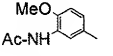
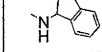
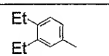
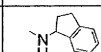
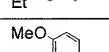
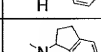
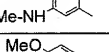
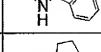
Ex	Syn	NR^3R^4	Dat	Sal
1	1		NMR2: 7.63-7.73 (2H, m), 4.52 (1H, m), 2.77-3.33 (4H, m); MP: 180-181	0.5 Fum
44	44		NMR2: 8.09-7.93 (2H, m), 7.76-7.64 (2H, m), 1.02 (3H, d, J=6.3 Hz); MP: 205-210	2 HCl 2 H_2O
187	5		NMR2: 7.08 (1H, dd, J = 8.3, 3.0 Hz), 6.98-6.94 (2H, m), 4.08-4.01 (1H, m); MP: 147-148	
188	1		NMR2: 7.93 (1H, t, J=7.8 Hz), 3.86 (3H, s), 2.09 (1H, m) MP: 173-176 (dec.)	Fum
189	3		NMR2: 1.10-1.13 (3H, m), 1.31-1.37 (3H, m), 2.44 (3H, s); MP: 134-135	
190	18		NMR2: 0.96-0.99 (3H, m), 3.82-3.84 (6H, m), 7.05-7.11 (2H, m); MP: 160-162	
191	18		NMR2: 0.95-0.98 (3H, m), 1.93-1.96 (2H, m), 3.81-3.84 (6H, m); MP: 124-127	3 H_2O
192	5		NMR2: 8.50 (1H, d, J=2.0 Hz), 3.83 (3H, s), 3.82 (3H, s), 1.33-1.14 (6H, m); MP: 93-99	
193	36		NMR1: 7.87-7.66 (3H, m), 3.06-3.03 (4H, m), 1.12-1.04 (3H, m); MP: 167-172	
194	21		NMR2: 3.81 (3H, s), 5.24 (2H, s), 8.58-8.60 (2H, m); MP: 171-174	

[0102]
[Table 15]

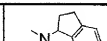
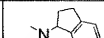
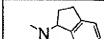
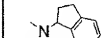
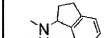
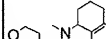
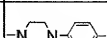
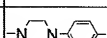
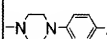
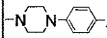
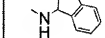
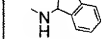
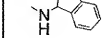
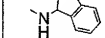
195	2		NMR1: 7.86 (1H, t, J=7.8 Hz), 4.71-4.65 (1H,m), 3.91(3H,s); MP: 220-223	
196	2		NMR1: 6.89 (1H, d, J=8.4Hz), 3.96 (3H, s), 3.63(1H,s); MP: 162-164	
197	2		NMR1: 7.73 (1H, m), 3.92 (3H, s), 3.29 (2H, m), F: 432	
198	5		NMR1: 7.74 (1H, dd, J=8.3, 1.0 Hz), 4.68 (1H,m), 3.94 (3H,s); MP: 144-146	
199	5		NMR1: 7.78(1H, dd, J= 7.8, 0.9 Hz), 3.95 (3H, s), 1.16 (3H, t, J=6.8Hz); F: 480	
200	5		NMR1: 7.71 (1H, m), 3.94 (3H, s), 2.86 (1H, m); F: 432	
201	5		NMR2: 3.01-3.12 (2H, m), 4.85-4.89 (2H, m), 8.39-8.42 (1H, m); MP: 77-79	

[0103]
[Table 16]



Ex	Syn	R^1, R^2	NR^3R^4	Dat	Sal
23	23			NMR1: 7.77(1H, dd, J=7.8, 1.0 Hz), 5.76(1H, q, J=8.3 Hz), 4.29(4H, s); MP:115-117	
24	24			NMR2: 8.00 (1H, dd, J= 7.8, 1.0Hz), 5.59(1H, q, J=8.3Hz), 2.42 (6H, s); MP: 155-157	Fum
25	25			NMR1: 7.80 (1H, dd, J= 7.8, 1.0Hz), 5.71(1H, q, J=7.8Hz), 5.20 (2H, s); MP: 129-131	
26	26			NMR2: 12.95 (0.4H, brs), 5.60 (1H, q, J= 8.5 Hz), 3.83 (3H, s); MP: 184-185	
27	27			NMR2: 5.59 (1H, q, J= 8.3 Hz), 3.81 (3H, s), 2.20 (6H, s); MP: 121-122	
28	28			NMR2: 7.13 (1H, d, J= 8.8 Hz), 5.60 (1H, q, J= 8.3 Hz), 3.88 (3H, s), 2.11 (3H, s); MP: 175-176	
29	29			NMR1: 7.91 (1H, t, J=7.8 Hz), 5.73 (1H, q, J=8.3 Hz), 2.01 (2H, q, J=8.3 Hz); F: 371	
30	30			NMR2: 5.56 (1H, q, J= 8.0 Hz), 3.82 (3H, s), 2.76 (3H, s); F: 374	Ox H_2O
31	31			NMR2: 5.61 (1H, q, J= 8.3 Hz), 4.01 (3H, s), 3.33 (6H, s); F: 388	HCl 2 H_2O
202	23			NMR2: 9.02 (1H, d, J= 8.8 Hz), 5.64 (1H, q, J= 8.8 Hz), 3.81 (3H, s); F: 345	HCl
203	23			NMR2: 9.05 (1H, d, J= 8.8 Hz), 5.63 (1H, dt, J= 8.3, 8.8 Hz), 3.83 (3H, s); F: 345	

[0104]
[Table 17]

204	23			NMR2: 9.11(1H, d, J=9.2Hz), 6.08 (2H, s), 5.65 (1H, dt, J=8.8, 9.2Hz); MP: 145-148	
205	5			F: 451	
206	5			F: 451	
207	5			NMR1: 7.91 (1H, t, J=7.8 Hz), 5.76 (1H, q, J=8.3 Hz), 2.32 (3H, s); F: 343	
208	5			FN: 388	
209	5			F: 500 MP: 154-157	Ox H_2O
210	5			NMR1: 7.76 (1H, dd, J= 8.3, 1.0Hz), 2.53 (3H, s), 0.32-0.38 (2H, m); MP: 142-144	
211	5			NMR1: 8.08 (1H, d, J= 2.5 Hz), 7.03 (1H, d, J=8.8Hz), 2.53 (3H, s); MP: 168-170	
212	5			NMR1: 7.07 (1H, d, J= 8.8 Hz), 6.62 (1H, t, J=74.8Hz), 2.54 (3H, s); MP: 160-162	
213	5			F: 529 MP: 168-170	
214	29			F: 361	
215	29			NMR1: 6.91 (1H, d, J= 8.2 Hz), 5.71(1H,s), 3.93 (3H, s)	
216	29			F: 360	
217	25			NMR2: 8.64(1H, d, J=1.5Hz), 3.93 (3H, s), 2.04-1.94(1H,m) MP: 137-138	

[Brief Description of the Drawings]

[0105]

[Drawing 1]The powder X diffraction figure of alpha type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Drawing 2]The thermometric analysis figure of alpha type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Drawing 3]The powder X diffraction figure of beta type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Drawing 4]The thermometric analysis figure of beta type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Translation done.]

TECHNICAL FIELD

[Field of the Invention]
[0001]
This invention relates to the medicine which makes a phenylpyridine derivative an active principle, especially 4 type phosphodiesterase (PDE4) inhibitor.

[Translation done.]

PRIOR ART

[Background of the Invention]
[0002]
The asthma considered as the reversible blockade of a respiratory tract so far became as [regard / now / as a disease characterized by the respiratory tract irritation and airway obstruction based on the chronic respiratory tract inflammation in which many inflammatory cells participate]. The increase of the patient number is being enhanced until now, and continuing to increase further is expected.
Inhalation steroid medicine is used as an antiinflammatory drug, and xanthine derivatives, such as beta stimulants, such as procaterol, and aminophylline, and theophylline, are mainly used for the asthmatic therapy as a bronchodilator now.
Although inhalation steroid medicine has extensive anti-inflammatory activity and the usefulness as asthma preparation is high, The suitable inhalation method's needing to be taught, existence of the asthmatic of steroid resistance, etc. are pointed out (ASTHMA 13-1, 69-73 (2000), internal medicine 81, and 485-490 (1998)).
A bronchodilator activates the adenylate cyclase which is a production enzyme of intracellular adenosine 3',5'-cyclic 1 phosphoric acid (cAMP) in an airway smooth muscle, Or by checking the phosphodiesterase (PDE) which is a dialytic ferment of cAMP, intracellular cAMP concentration is raised and the remission of the contraction of an airway smooth muscle is carried out (internal medicine 69 and 207-214 (1992)). it is known that the rise of intracellular cAMP concentration will cause control of contraction in an airway smooth muscle (Clin. Exp. Allergy and 22,337-344 (1992).) It is effective in an improvement of Drugs of the Future, 17, 799-807 (1992), and the shape of asthma.
however, the thing (J. Cyclic Nucleotide and Protein Phosphorylation Res., 10, and 551-564 (1985).) for which a xanthine derivative reveals systemic side effects, such as a blood pressure fall and a strong heart operation J. If Pharmacol. Exp. Ther., 257, 741-747 (1991), and beta stimulant tend to produce hyposensitization and the amount used increases, producing side effects, such as a finger tremor and palpitation, is known.
[0003]
On the other hand, a chronic obstructive pulmonary disease (COPD) is a respiratory illness characterized by the air current restrictions relevant to an unusual inflammatory response which are not reversible.
Now, it is supposed that it is the 4th place of the cause of death in the world (2000). (Executive summary. Global Initiative for Chronic Obstructive Lung Disease (GOLD))
As pharmacotherapy to COPD, a bronchodilator called xanthine derivatives, such as beta stimulant, an anticholinergic drug, aminophylline, and theophylline, is generally used like asthma now. Since it attracts attention that existence of the chronic inflammation in a respiratory tract is participating in obstructive impairment greatly also in COPD, inhalation steroid medicine

is also used, but. The continuous therapy by inhalation steroid FEV1 of a COPD patient. not improving the long-term fall of (forced expiratory volume in one second) is reported (N. Engl. J. Med. 340 and 1948-53 (1999).) It is anxious for Lancet 353, 1819-23 (1999), BMJ 320, 1297-303 (2000), N. Engl. J. Med. 343, 1902-9 (2000), and the antiinflammatory drug that can improve the symptoms of COPD.

[0004]

PDE was classified into seven families of PDE 1-7 at least, and it has been solved that distribution or a function has a difference, respectively (Prog. Nucleic Acid Res. Mol. Biol. 63 and 1-38 (1999)). Especially PDE4 decomposes cAMP specifically, without acting on guanosine 3',5'-cyclic 1 phosphoric acid (cGMP) also in a nucleotide.

The existence is accepted by both an airway smooth muscle and infiltrating cells.

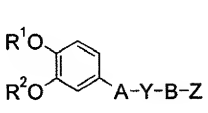
As opposed to the eosinophil leukocytic infiltrate by an antigen and a platelet activating factor, [in / in PDE4 inhibitor / a guinea pig] Depressant action is shown (Eur. J. Pharmacol., 255, and 253-256 (1994)), What (Br. J. Pharmacol., 115, 39-47 (1995)) isolation of the obstacle nature protein (MBP, ECP) from eosinophile leucocyte is controlled for is reported. Furthermore, depressant action is shown to contraction of the airway smooth muscle by the quality of shrink material (histamine, a mesa choline, LTD_4) (Br. J. Pharmacol., 113, and 1423-1431 (1994)), Production of IL-4 which is cytokine said to participate in asthma deeply is checked (J. Invest. Dermatol., 100, and 681-684 (1993)), Depressant action is revealed to sthenia of the blood vessel permeability in a respiratory tract (Fundam. Clin. Pharmacol., 6, 247-249 (1992)), It is reported that depressant action is shown to a respiratory tract anaphylaxis (Eur. J. Pharmacol., 275, 75-82 (1995)). Therefore, PDE4 inhibitor is expected as an asthmatic treating agent.

Furthermore, having permeation depressant action to the neutrophil leucocyte it is supposed that is participated in the respiratory tract inflammation in COPD (Pulm. Pharmacol. Ther. 2001 Mar; 14(2):157-164) is reported by PDE4 inhibitor, and again, Also in the clinical trial, it is shown that a COPD patient's respiratory function can be improved (Clin. Exp. Allergy. 1999 Jun; 29 Suppl 2:99-109), and PDE4 inhibitor is expected also as a COPD remedy.

[0005]

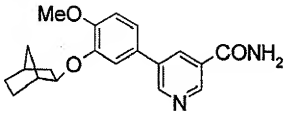
The following compound is indicated by the patent documents 1 as a compound which has PDE4 inhibiting activity.

[Formula 2]

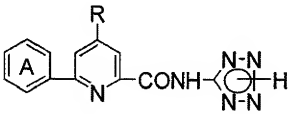


[A, Y, and B among a formula the pyridine ring etc. in which Z may be replaced by R^3 in combination etc., R^3 means $CONR^4R^5$ etc. and R^4 H, The phenyl which may be replaced with C_{1-6} alkyl, C_{1-4} alkyl, or halogen, $CH(R^7)$ CO_2R^6, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl or C_{2-5} alkylene dialkylamino (the carbon number of the dialkylamino part concerned is five or less pieces at all), R^5 H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, phenyl, pyridyl, pyrimidyl, Thiazolyl, oxazolyl or R^4, and R^5 with the nitrogen atom to combine C_{1-4} alkyl of 1 thru/or 2 (1), As the saturation or the unsaturation 5 which may be replaced by the basis chosen from CO_2R^7, $CONH_2$, $CON(CH_3)_2$, oxo, OH, NH_2, and $N(CH_3)_2$ - 6 member heterocycle, and a (2) ring atom, further O, S, The saturation which has one hetero atom chosen from N (H), N (CH_3), N ($COCH_3$), or N (CH_2 Ph), unsaturation 6 member heterocycle, or the quinoline ring which may

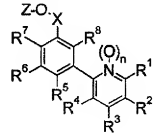
be replaced with (3) fluoride is shown.]
However, although a phenylpyridinecarboxamide derivative is included in an extensive claim of the gazette concerned, a compound which has a statement concretely is only the following 5-phenylpyridine- 3-carboxamide.
[Formula 3]



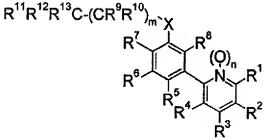
[0006]
It is indicated by the patent documents 2 as a 6-phenylpyridine- 2-carboxamide derivative that the following compound has an antiallergic action.
[Formula 4]



(R shows among a formula the phenyl group which has a substituent as which A is chosen from phenyl, halogen, low-grade alkyl, and low-grade alkoxy ** nitro and OH in hydrogen, halogen, and low-grade alkoxy ** 1-3.)
However, there is no statement about the PDE4 inhibiting activity of the compound concerned.
[0007]
Although the following phenylpyridinecarboxamide derivative which has a herbicidal action and a vegetable drying effect in the patent documents 3 and the patent documents 4 is indicated, neither an indication nor suggestion is about PDE4 inhibitory action.
[Formula 5]

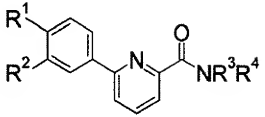


,

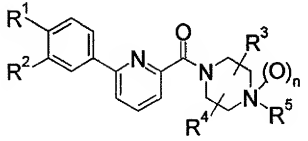


(R^1 shows $CONH_2$, CONH (C_{1-4} alkyl), $CON(C_{1-4}$ alkyl$)_2$, etc. among a formula.) Others are concerned referring to the gazette.
[0008]
As a phenylpyridinecarboxamide derivative which has PDE4 inhibiting activity, it is the

following compound to the patent documents 5.
[Formula 6]



(Among a formula, R^3 is set to the low-grade alkenyl etc., R^4 sets H, low-grade alkyl, etc. to NR^3R^4, and R^1 and R^2 H, halogen, low-grade alkyl, and O-low-grade alkyl etc.) The nitrogen-containing heterocycle which is united with N which R^3 and R^4 combine, and may be replaced is shown. It is concerned referring to the gazette for details. It is the following compound to the patent documents 6.
[Formula 7]



(R^1 and R^2 show H, halogen, low-grade alkyl, and O-low-grade alkyl etc. among a formula, and R^5 shows H, low-grade alkyl, etc.) It is concerned referring to the gazette for details. Although indicated, respectively, the patent documents 5 and 6 are the literature exhibited by each after this application priority date.
[0009]
[Patent documents 1] The international publication 94th/No. 12461 pamphlet
[Patent documents 2] JP,56-7782,A
[Patent documents 3] The international publication 96th/No. 21645 pamphlet
[Patent documents 4] The international publication 96th/No. 21646 pamphlet
[Patent documents 5] JP,2003-64057,A
[Patent documents 6] The international publication 02nd/No. 102778 pamphlet

---

[Translation done.]

EFFECT OF THE INVENTION

[Effect of the Invention]
[0012]
Since the new pyridine- 2-carboxamide derivative which has a phenyl group in the 6th place shown by after-mentioned type (I) is excellent in the inhibiting activity of PDE4, the medicinal composition containing the compound concerned, It is useful as prevention and a treating agent of the respiratory illnesses (for example, bronchial asthma (atopic asthma is included), COPD, chronic bronchitis, a pneumonia nature disease, adult respiratory distress syndrome (ARDS), etc.) in which PDE4 participates. It is especially expectable as bronchial asthma, and prevention and the remedy of COPD. The disease of others by which the intervention of PDE4 is known as for the medicinal composition concerned, For example, the disease in which cytokine (IL-1, IL-4, IL-6, and TNF (tumor necrosis factor)) etc. participate. for example, articular rheumatism, ulcerative colitis, Crohn's disease, septicemia, and the septic shock. endotoxin shock, gram-negative-bacteria septicemia, toxic shock syndrome, a nephritis, hepatitis, infection (bacteria and virus), circulatory failure (cardiac insufficiency, arteriosclerosis, myocardial infarction, cerebral apoplexy), etc. -- etc. -- it is useful also as prevention and a remedy.
The crystal especially alpha type, and beta type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine of this invention are excellent in stability, and useful as a manufacture field object of the medicinal composition of this invention. beta type crystal fits the extensive composition in industrial production especially.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention]

[0010]

This invention persons could administer orally, checked PDE4 good and selectively, and inquired for the purpose of providing a useful medicinal composition and providing the medicine which contains these further for prevention and the therapy of respiratory illnesses, such as bronchial asthma with few side effects, and COPD.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

MEANS

[Means for Solving the Problem]
[0011]
This invention persons took lessons from a compound which has inhibiting activity to PDE4, and inquired wholeheartedly. As a result, the knowledge of having PDE4 inhibitory action powerful [a new pyridine- 2-carboxamide derivative which has a phenyl group], and alternative was carried out to the 6th place, and this invention was completed.

[Translation done.]

EXAMPLE

[Example]

[0039]

Hereafter, although an example explains this invention concretely, these do not limit the range of this invention. The process of the phenylpyridine derivative which is a medicinal active principle of this invention is shown in the example of manufacture, and the process of the raw material compound of the compound concerned is shown in a reference example.

Example 1 (PDE4 inhibiting activity)

1) The solution containing PDE4 was refined from the rat ventricle muscle as follows. The physiological saline separated the ventricle for the heart extracted under anesthesia from male Wistar rats after washing. the buffer solution A (20 --) which comes out on both sides of the separated ventricle, cuts finely, and contains PROTEASE INHIBITOR COCKTAIL For Mammalian Cell Extracts (SIGMA) for this 1% [mM Bis-Tris and] 50 mM sodium acetate, 2 mM EDTA, and 5 mM 2-mercaptoethanol, 2 The cell was destroyed by polyTRON after being suspended to mM benzamidene, 0.05 mM phenyl-methyl-sulfonyl-fluoride, and pH 6.5, and the soluble fraction was obtained by carrying out ultracentrifuge (for 100,000 G and 60 minutes, 4 **).

2) The 2.6x10 cm Q sepharose column equilibrated with the buffer solution A was filled up with the obtained soluble fraction. Subsequently, this column was washed by buffer solution A 1200 ml, and uncombined protein was removed. The protein combined with this column was eluted using buffer solution A 750 ml containing the linearity inclination liquid of 0.05 - 1.00 M sodium acetate, and 110 7 ml fractionation was collected. It inspected about the cAMP metabolic turnover PDE activity of each fractionation obtained under cGMP and calcium / calmodulin existence, or nonexistence. The fractionation which has the metabolic activity of cAMP in each fractionation and in which cAMP metabolic activity does not receive influence by existence of cGMP, or calcium/calmodulin was used as a stock solution for inspecting PDE4 inhibiting activity.

A test compound the concentration of a request 3) 40 mM Tris-HCl (pH 8.0), 5 mM magnesium chloride, 4 mM 2-mercaptoethanol, 1microM cAMP, and 1 muCi/ml It was made to react for 10 minutes at 30 ** in the reaction mixed liquor which [^{3}H] cAMP and PDE4 stock solution contains. 18 mM sulfate of zinc of a moiety [reaction mixture], 5 Add the 20 mg/ml Polylysine coated yttrium silicate SPA beads (Amersham)

suspension containing muM 3-ISOBUTYL-1-METHYLXANTHINE (IBMX), and stop a reaction, Radioactivity was measured.

IC_{50} considered it as the test compound concentration which checks the metabolic activity of PDE4 50%, and computed about each compound.

The above-mentioned examining method and the method given in WO97/19078 gazette were applied, and PDE1, PDE2, PDE3, and PDE5 inhibiting activity was measured similarly.

Compound (I) shows good inhibiting activity to PDE4 as a result of the above-mentioned measurement, The compound of the examples 2, 4, 5, 36, 48, 57, 75, 82, 96, 99, 137, 164, 171, 180, 191, 199, and 210 of the after-mentioned manufacture showed the powerful activity below of 12 nM in IC_{50} especially. The concentration hardly showed inhibiting activity to PDE1, PDE2, PDE3, and PDE5. Therefore, it was checked that it is PDE4 inhibitor whose compound (I) was alternative and which was excellent.

[0040]

Example 2 (oral absorbency evaluation test which made TNF-alpha production inhibiting activity the index)

1) Test compound 10 mg/kg suspended to methyl cellulose purified water 0.5% was administered orally to the 8-weeks old male Fischer rat. The control group was similarly medicated with the solvent (0.5% methyl cellulose purified water, 3 ml/kg). After internal use, from the caudal vein of the rat which performed anesthesia temporally, it collected blood under heparin existence and plasma was prepared in accordance with the conventional method.

2) So that the whole quantity per hole may be set to 200microl at 96 hole culture plate, Whole blood 20mul of the plasma (2.5% of the last concentration) prepared in the top, RPMI1640 culture medium which contains fetal calf serum 10%, and male Wistar rats, and LPS (the 3 microg/ml last concentration) were poured distributively, and it cultivated at 37 ** overnight using CO_2 incubator. Centrifugality (for 1500 r.p.m. and 10 minutes) of the plate was carried out after the end of culture, supernatant liquid was collected, and the amount of TNF-alpha in supernatant liquid was measured using commercial ELISA kit.

It became clear that the example compound of manufacture had good oral absorbency as a result of the above-mentioned examination.

It is clear that compound (I)'s it is useful as the prevention and a remedy of a disease in which it is checked as a result of the above-mentioned inhibiting activity measurement test that alternative and powerful inhibiting activity is shown to PDE4, and PDE4 involves since oral absorbency is also good.

[0041]

Example 3 (operation on the eosinophil leukocytic infiltrate in an antigen induction rat respiratory tract)

Antigen sensitization was performed to a 4-weeks old Brown Norway system feminity rat (Japanese CHARU sliver, Kanagawa) by continuing for three days and carrying out 1 ml intraperitoneal injection of the OA solution for sensitization (the last concentration: OA;1 mg/ml, $aluminum(OH)_3$;20 mg/ml) per animal. The administration first day was set to Day 0. 1%OA / physiological salt solution was atomized with the ultrasonic nebulizer (NE-U12, OMRON) to Day 21 or 22, antigen exposure was carried out by making a sensitization rat inhale for 20 minutes, and permeation of the eosinophile leucocyte into a respiratory tract was caused. The group which carried out inhalation exposure of the physiological salt solution was used as a normal

control group. It was suspended in MC solution 0.5%, and the test compound was administered orally 1 hour before the antigen inhalation exposure start. From the day preceding antigen inhalation exposure, the animal was considered as the fast and canceled the fast after antigen inhalation exposure. After making an incision in the abdomen under the Nembutal anesthesia and carrying out bleeding fatality of the animal from an abdominal aorta 24 hours after antigen inhalation exposure, By inserting cannula (6 Fr-atom catheterization of vein, atom) in a trachea, and repeating operation of pouring in and collecting the heparin (1 unit/ml) content physiological salt solutions of 2 ml, 5 times (a total of ten ml(s)), Broncho-alveolar lavage (BAL:Bronchoalveolar Lavage) was performed. Supernatant liquid was removed for the collected BAL liquid after centrifugality by 500xg (for 4 ** and 10 minutes), and the dregs (cell fraction) were re-suspended with a heparin (1 unit/ml) content physiological salt solution of 500microl. After measuring the total leukocyte concentration of re-suspension with blood cell counters (Celltac-alpha, Nihon Kohden), the smear was produced, it observed under the microscope after dyeing with the blood stain solution for differentiation (DIFU quick, International Reagents), and the rate of an abundance ratio of eosinophile leucocyte was computed from the morphological feature. From the total white blood cell count and the rate of an eosinophile leucocyte abundance ratio, the total of the number of eosinophile leucocytes was computed and the effect of the drug was evaluated.

The compound of the examples 2, 36, and 180 of manufacture showed 60%, 92%, and 31% of inhibiting activity in internal use of 3.0 mg/kg, respectively as a result of the above-mentioned measurement. Although the compound (compound A) of the example 36 of manufacture used alpha type crystal in the exam, since alpha type crystal and beta type crystal have almost equivalent solubility to water and pH 1.2 or pH 6.8 buffer solution, beta type crystal is considered to be effective the same way.

[0042]

Example 4 (operation on the neutrophilic infiltration in a rat LPS induction respiratory tract)

the 6-weeks old Wistar system male rat (Japanese CHARU sliver.) which anesthetized by injecting intraperitoneally optimum dose of ketamine / KISHIRAJIN mixed liquor 10 microg [which was dissolved in a physiological salt solution in Kanagawa]/ml LPS Permeation of the neutrophil leucocyte into a respiratory tract was caused by prescribing a solution (Lipopolysaccharide E.coli 0127:B8 Boivin, DIFCO) for the patient in a respiratory tract using a 200microl sound. The group which prescribed a physiological salt solution for the patient in the respiratory tract was used as a normal control group. It was suspended in MC solution 0.5%, and the test compound was administered orally 1 hour before the administration in an LPS respiratory tract. From the day preceding the administration in an LPS respiratory tract, the animal was considered as the fast and canceled the fast after the administration in an LPS respiratory tract. 24 hours after the administration in an LPS respiratory tract, after making an incision in the abdomen under the Nembutal anesthesia and carrying out bleeding fatality of the animal from an abdominal aorta, the total leukocyte concentration was measured like the following above-mentioned example 3. The rate of an abundance ratio of neutrophil leucocyte was similarly computed from the morphological feature observed under the microscope. From the total white blood cell count and the rate of a neutrophil leucocyte abundance ratio, the total of the number of neutrophil leucocytes was computed and the effect of the drug was evaluated.

[0043]

The cable address below the inside of a reference example and the after-mentioned table is used. the

example number of Ex:manufacture, and Dat:physicochemical data (F:FAB-MS(M+H) $^{+}$.) FN:FAB-MS(M-H) $^{-}$, EI:EI-MS (M^{+}), AP:APCI-MS(M+H) $^{+}$, MP : delta (ppm) of the characteristic peak in ^{1}H NMR in melting point (**) NMR1:$CDCl_3$, NMR2: delta (ppm) of the characteristic peak in ^{1}H NMR in DMSO-d_6, RT: HPLC (Wakosil-II 5C18AR 2.0 x 30 mm, 5 mM TFAaq / MeOH = 9/1(0 min)-0/10(7.5min)-0/10(8 min), 1.2 ml/min, 35 **, 254 the retention time (min) in nm, a Sal:salt, and a content solvent (Ox: -- an oxalate.) Fum: Fumaric acid chloride, a blank :. As for the number in front of a free object and an ingredient, for example, 2 HCl shows two hydrochlorides. Syn: -- a manufacturing method (a number shows the example number of manufacture manufactured similarly), and Me: -- methyl, Et:ethyl, iPr:2-propyl, cPr:cyclopropyl, tBu:t-butyl, cHex:cyclohexyl, and Ph:phenyl -- Bn:benzyl. Ac: Acetyl, Pip:piperidine- 1-yl, Pip4:piperidine- 4-yl, Mor:morpholine-4-yl, Pipr:piperazine 1-yl, Pyrr:pyrrolizine-1-yl, 4-Me-Pipr:4-methylpiperazine-1-yl. moreover -- the number in front of a substituent shows replacement positions -- for example, 2-Cl -- 2-chloro -- 3,4-diMe expresses 3,4-dimethyl, 2,3,4-triMe expresses 2,3,4-TORIMECHIRU, and 3,4- (OCH_2O) expresses a 3,4-methylenedioxy group, respectively.

MAC Science MXP18TAHF22 is used for measurement of a powder X diffraction, Bulb: It measured on conditions (Cu, tube current:120 mA, tube voltage:50 kV, sampling width:0.020 degree, scan speed:3 degrees /, min, wavelength:1.54056A, and measurement angle-of-diffraction range (2 theta):5-40 degree). Thermometric analysis (DSC and TGA) was measured on the following conditions, respectively.

DSC:TA Instrument TA 5000, room temperature -400 ** (10 ** / min), N2 (50 ml/min), the thump lupane made from aluminum. TGA:TA Instrument TA 5000, room temperature -400 ** (10 ** / min), N2 (100 ml/min), the thump lupane made from platinum.

[0044]

Reference example 1

Add palladium acetate, triphenyl phosphine, and sodium carbonate to the mixture of 6-chloropyridine- 2-methyl carboxylic acid, 3,4-dimethoxyphenylboric acid, dimethoxyethane, and water, and it reacts to it at 100 ** for 1 hour, 6-(3,4-dimethoxyphenyl) pyridine- 2-methyl carboxylic acid was obtained. Among the THF-methanol mixed solution, 1M sodium hydroxide solution was added, the obtained compound was reacted for 30 minutes under heating at 60 **, and 6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid was obtained. NMR2: 8.18 (1H, d, J=8.0 Hz), 7.09 (1H, d, J=8.0 Hz), 3.87;(3H, s) F : 260.

Reference example 2

4-carbomethoxy benzophenone oxime which added hydroxylamine hydrochloride to the pyridine solution of 4-methyl o-benzoylbenzoate, was made to react to it under heating, and was obtained, It was made to react among methanol and under palladium carbon existence and a hydrogen atmosphere, and 4-(alpha-aminobenzyl) methyl benzoate was obtained. F: 242.

Reference example 3

At -78 **, n-butyl lithium / n-hexane solution was added to the THF solution of the 4-bromo-2-chloroanisole, and it stirred in it for 30 minutes. Subsequently, trimethyl borate was added, and to the room temperature, temperature up was carried out and it stirred for 30 minutes. The residue produced by distilling off a solvent was used instead of 3,4-dimethoxyphenylboric acid, and 6-(3-chloro-4-methoxypheny) pyridine- 2-carboxylic

acid was obtained like the reference example 1. FN: 262.

[0045]

Reference example 4

6-(3-fluoro-4-methoxypheny) pyridine- 2-carboxylic acid was manufactured like the reference example 3. FN: 246.

Reference example 5

6-(3-benzyloxy 4-methoxypheny) pyridine- 2-carboxylic acid was manufactured like the reference example 3. NMR1: 6.95-7.05 (1H, m), 5.28 (2H, s), 3.95 (3H, s).

Reference example 6

6-(4-benzyloxy 3-methoxypheny) pyridine- 2-carboxylic acid was manufactured using 1-benzyloxy 4-bromo-2-methoxybenzene like the reference example 3 (however, hydrolysis was performed for 2.5 days at 100 ** among 1M sodium hydroxide solution). F: 336.

Reference example 7

Added concentrated hydrochloric acid and platinum oxide to the ethanol solution of N,N-diethylquinolin-2-carboxamide, it was made to react for bottom three days of a hydrogen atmosphere of 3 atmospheres, and N,N-diethyldecahydronaliumquinolin-2-carboxamide was obtained. F: 239.

Reference example 8

6-(3,4-dimethoxyphenyl) pyridine- 2-carboxylic acid and t-butoxycarbo NIRUPI perazine are used, Obtain a 1-{[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl]-4-(t-butoxycarbonyl) piperazine by the same method as the below-mentioned example 2 of manufacture, and add 4M hydrogen chloride / ethyl acetate solution further, and it reacts, The 1-{[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine was obtained. F: 328.

[0046]

Reference example 9

The bottom pyridine of ice-cooling and chloroacetyl chloride were made to add and react to the acetonitrile fluid of a 1-amino-1,2,3,4-tetrahydronaphthalene, and the 2-chloro-N-(1,2,3,4-tetrahydronaphthalene 1-yl) acetamide was obtained. Cesium carbonate and morpholine were added to the acetonitrile fluid of the obtained compound, it stirred at the room temperature for 17 hours, and the 2-(morpholine-4-yl)-N-(1,2,3,4-tetrahydronaphthalene 1-yl) acetamide was obtained. Lithium hydride aluminum was added to the THF solution of the obtained compound under ice-cooling, heating flowing back was carried out for 30 minutes, and N-[2-(morpholine-4-yl) ethyl]-1,2,3,4-tetrahydronaphthalene 1-ylamine was obtained as dihydrochloride. F: 261.

Reference example 10

To the toluene solution of 2-bromotoluene, 1-(t-butoxycarbonyl)-1,4-JIAZEPAN, Add tris(dibenzylidene acetone)dipalladium (0)2,2'-bis(diphenylphospino)-1,1'-binaphthyl and sodium t-butoxide, and it stirs at the oil bath temperature of 80 ** for 15 hours, 1-(t-butyloxy carbonyl)-4-(2-methylphenyl)-1,4-JIAZEPAN was obtained. 4M hydrogen chloride / ethyl acetate solution was added to the methanol solution of the obtained compound, it stirred at the room temperature for 4 hours, and 1-(2-methylphenyl)-1,4-JIAZEPAN was obtained as dihydrochloride. F: 191.

Reference example 11

the acetic acid solution of 1-(ethoxycarbonyl) piperidine- 4-one -- 3-chloroaniline and hydrogenation -- doria -- SETOKISHIHOU -- base -- sodium was added, it stirred for 30 minutes at the room temperature, and the 4-(3-chlorophenylamino)-1-(ethoxycarbonyl) piperidine hydrochloride was obtained. Concentrated hydrochloric acid was added to the obtained compound, it stirred for two days at the oil bath temperature of 100 **, and 4-(3-chlorophenylamino) piperidine dihydrochloride was obtained. F: 211.

[0047]

Reference example 12

1-benzylisonipecotic acid ethyl was added to the THF solution of lithium diisopropylamide at -78 **, and it stirred at -78 ** for 1 hour. The methyl iodide was added to reaction mixture and it stirred for 30 minutes at -78 **, and it stirred for 1 hour, carrying out temperature up to a room temperature further gradually, and 1-benzyl-4-methyl isonipecotic acid ethyl was obtained. The obtained compound was stirred for 3.5 days at the oil bath temperature of 100 ** among 3M hydrochloric acid aqueous solution, and the 1-benzyl-4-methyl isonipecotic acid hydrochloride was obtained. Subsequently, the diphenyl azide phosphoryl and triethylamine were added among toluene, and heating flowing back of the obtained compound was carried out for 30 minutes. 2-(trimethylsilyl) ethanol was added to reaction mixture, it stirred at the oil bath temperature of 110 ** for 14 hours, and N-[2-(trimethylsilyl) ethoxycarbonyl]-1-benzyl-4-methyl-4-piperidyl amine was obtained. F: 349.

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[0105]

[Drawing 1]The powder X diffraction figure of alpha type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine-2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Drawing 2]The thermometric analysis figure of alpha type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Drawing 3]The powder X diffraction figure of beta type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine-2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Drawing 4]The thermometric analysis figure of beta type crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Translation done.]

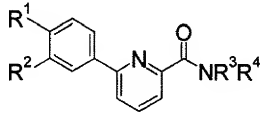
* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1]
A medicinal composition comprising:
A pyridine derivative shown by general formula (I), or its salt permitted pharmaceutically.
A carrier permitted pharmaceutically.

[Formula 1]



(I)

(The sign in a formula shows a following meaning.)

R^1 and R^2 : Differ identically or mutually and H, halogen, Low-grade alkyl and O-low-grade alkyl, O- (low-grade alkyl replaced with halogen), NH_2, NH-low-grade alkyl, N(low-grade alkyl) $_2$, NHCO-low-grade alkyl, O-low-grade alkylene NH-low-grade alkyl, O-low-grade alkylene N(low-grade alkyl) $_2$, O-low-grade alkylene CO_2R^0, an O-low-grade alkylene hydrocarbon ring, O-low-grade alkylene heterocycle or R^1, and R^2 are united, and it is the -O-low-grade alkylene O. -

R^0: H, low-grade alkyl, or CH_2 - (phenyl which may be replaced)

R^3 : A low-grade alkenyl, low-grade alkynyl, and hydrocarbon ring which may be replaced, Heterocycle which may be replaced, a hydrocarbon ring by which low-grade alkylene substitution may be carried out, Heterocycle, low-grade alkylene R^{51} by which low-grade alkylene substitution may be carried out, Low-grade alkylene CO_2R^0, low-grade alkylene $N(R^0)$-low-grade alkyl, $C(R^{53})$ (R^{54})-R^{55}, low-grade alkylene C (R^{53}) (R^{54})-R^{55}, or O-R^0,

R^4: H, low-grade alkyl, low-grade alkenyl, low-grade alkynyl, A hydrocarbon ring which may be replaced, heterocycle which may be replaced, A hydrocarbon ring by which low-grade alkylene substitution may be carried out, heterocycle by which low-grade alkylene substitution may be carried out, Low-grade alkylene R^{51}, low-grade alkylene CO_2R^0, Low-grade alkylene $N(R^0)$-low-grade alkyl, $C(R^{53})$ (R^{54})-R^{55}, or low-grade alkylene $C(R^{53})$ (R^{54})-R^{55},

R^{51}: CO-low-grade alkyl, CO- (hydrocarbon ring which may be replaced), CO- (heterocycle which may be replaced), and CO-low-grade alkylene (hydrocarbon ring which may be replaced), CO-low-grade alkylene (heterocycle which may be replaced), CN, OH, O-low-grade alkyl, O- (hydrocarbon ring which may be replaced), O- (heterocycle which may be replaced), and O-low-grade alkylene (hydrocarbon ring which may be replaced), O-low-grade alkylene (heterocycle which may be replaced), S-low-grade alkyl, S- (hydrocarbon ring which may be replaced), S- (heterocycle which may be replaced), S-low-grade alkylene (hydrocarbon ring which may be replaced), S-low-grade alkylene (heterocycle which may be replaced), NH (R^0), $N(CH_3)_2$, $N(C_2H_5)_2$, $N(R^0)$- (hydrocarbon ring which may be replaced), $N(R^0)$- (heterocycle which may be replaced), $N(R^0)$-low-grade alkylene (hydrocarbon ring which may be replaced), $N(R^0)$-low-grade alkylene (heterocycle which may be replaced). $N(R^0)$ CO-low-grade alkyl, $N(R^0)$ CO- (hydrocarbon ring which may be replaced), $N(R^0)$ CO- (heterocycle which may be replaced), and $N(R^0)$ CO-low-grade alkylene (hydrocarbon ring which may be replaced), $N(R^0)$ CO-low-grade alkylene (heterocycle which may be replaced), $N(R^0)$ CO-O-low-grade alkyl, $N(R^0)$ CO-O-low-grade alkylene (hydrocarbon ring which may be replaced), or $N(R^0)$ CO-O-low-grade alkylene (heterocycle which may be replaced),

R^{53}, R^{54}, and R^{55}: Differ identically or mutually and they are H, low-grade alkyl, and CO_2R^0, CON (R^0) (R^{56}), R^{51}, or R^{56},

R^{56}: A hydrocarbon ring which may be replaced, heterocycle which may be replaced, a hydrocarbon ring by which low-grade alkylene substitution may be carried out, heterocycle by which low-grade alkylene substitution may be carried out, low-grade alkylene R^{51}, or low-grade alkylene CO_2R^0,

Or nitrogen-containing heterocycle which is united with N which R^3 and R^4 combine, and may be replaced in NR^3R^4.

However, the following compounds are excluded. :

(1) When R^4 is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, phenyl, pyridyl, pyrimidyl, thiazolyl, or oxazolyl, R^3 C_{1-6} alkyl, (phenyl which may be replaced with C_{1-4} alkyl or halogen), $CH(R^{00})$ CO_2R^{00}, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, the C_{2-5} alkylene N (CH_3) (C_4H_9). Or a compound which is the C_{2-5} alkylene N (C_2H_5) (C_3H_7) (R^{00} differs identically or mutually and is H or C_{1-4} alkyl.),

When R^4 is H, R^3 (2) OH, C_{1-6} alkyl, (Phenyl which may be replaced with C_{1-4} alkyl or halogen), $CH(R^{00})$

CO_2R^{00}, C_{3-7} cycloalkyl, C_{1-4} alkylene phenyl, the C_{2-5} alkylene N (CH_3) (C_4H_9). a compound which is the C_{2-5} alkylene N (C_2H_5) (C_3H_7), pyridyl, pyrimidyl, thiazolyl, oxazolyl, or tetra ZORIRU -- and

(3) Nitrogen-containing heterocycle formed in NR^3R^4 united with N which R^3 and R^4 combine, (i) 1 thru/or 2 C_{1-4} alkyls, CO_2R^{00}, $CONH_2$, $CON(CH_3)_2$, oxo, It may be replaced by OH, NH_2, or $N(CH_3)_2$, 1-pyrrolidyl or 1-piperidyl by which desaturation may be carried out; (ii). Desaturation may be carried out. 4-morpholinyl or thio morpholine-4-yl; -- 1 by which (iii) 4 place may be replaced by methyl, acetyl, or benzyl, and desaturation may be carried out - PIPERAJIRU; or a quinoline ring which may be replaced by (iv) F -- coming out -- a certain compound.

[Claim 2]

The medicinal composition according to claim 1 which is 4 type phosphodiesterase inhibitor.

[Claim 3]

The medicinal composition according to claim 2 which is prevention or a treating agent of a respiratory illness.

[Claim 4]

The medicinal composition according to claim 3 which is prevention or a treating agent of bronchial asthma.

[Claim 5]

The medicinal composition according to claim 3 which is prevention or a treating agent of a chronic obstructive pulmonary disease (COPD).

[Claim 6]

The medicinal composition according to claim 1 whose pyridine derivative is 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Claim 7]

The medicinal composition according to claim 6 which is solid preparations.

[Claim 8]

A crystal of 4-(4-{4-[6-(3,4-dimethoxyphenyl) pyridine- 2-carbonyl] piperazine 1-yl} phenyl) morpholine.

[Claim 9]

The crystal according to claim 8 which has a peak of 2theta(degree) 10.82, 12.86, 16.96, 19.90, and 21.76 and 22.88 by a powder X diffraction.

[Claim 10]

The crystal according to claim 8 which has a peak of 2theta(degree) 11.66, 14.92, 16.92, 19.44, 20.10, and 21.06 and 21.90 by a powder X diffraction.

[Claim 11]

The crystal according to claim 8 which has a heat-absorptive peak (extrapolation starting temperature (onset)) at 140-143 ** by DSC analysis.

[Claim 12]

The crystal according to claim 8 which has a heat-absorptive peak (extrapolation starting temperature (onset)) at 128-131 ** by DSC analysis.

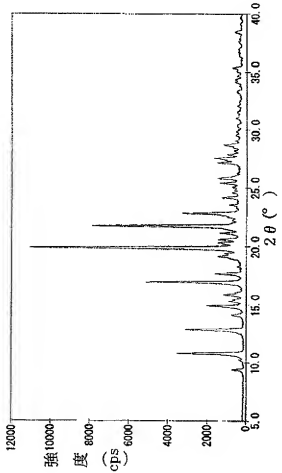
[Translation done.]

* NOTICES *

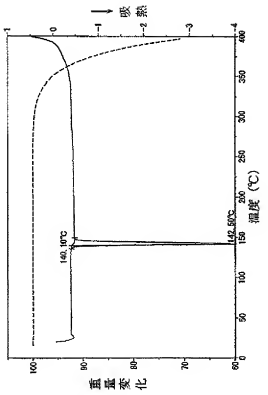
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DRAWINGS

[Drawing 1]



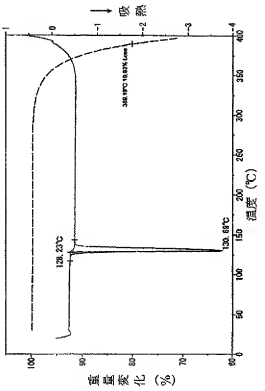
[Drawing 2]



[Drawing 3]

8000
7000
6000
5000
4000
3000
2000
1000
0
強度(cps)
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
2θ(°)

[Drawing 4]



[Translation done.]